COAGULATION PROFILE STUDY IN PREGNANCY INDUCED HYPERTENSION

Dissertation submitted in

Partial fulfilment of the regulations required for the award of

M.D.DEGREE

IN

PATHOLOGY

THE TAMILNADU

DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL, 2015

DECLARATION

I hereby declare that the dissertation entitled "**COAGULATION PROFILE STUDY IN PREGNANCY INDUCED HYPERTENSION"** is a bonafide research work done by me in the Department of Pathology, Coimbatore Medical College during the period from July 2013 to July 2014 under the guidance and supervision of **Dr.A.Arjunan, M.D.,** Professor, Department of Pathology, Coimbatore Medical College.

This dissertation is submitted to The TamilnaduDr.MGR Medical University, Chennai towards the partial fulfilment of the requirement for the award of M.D., Degree (Branch III) in Pathology. I have not submitted this dissertation on any previous occasion to any University for the award of any Degree.

Place: Coimbatore

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CERTIFICATE

This is to certify that the dissertation entitled "**COAGULATION PROFILE STUDY IN PREGNANCY INDUCED HYPERTENSION"** is a record of bonafide work done by **Dr. S.VIJAYALAKSHMI** in the Departmentof Pathology, Coimbatore Medical College, Coimbatore under the guidance and supervision of **Dr. A. ARJUNAN M.D.,** Professor, Department of Pathology, Coimbatore Medical College and submitted in partial fulfilment of the requirements for the award of M.D. Degree (Branch III) in Pathology by The TamilnaduDr. MGR University Chennai.

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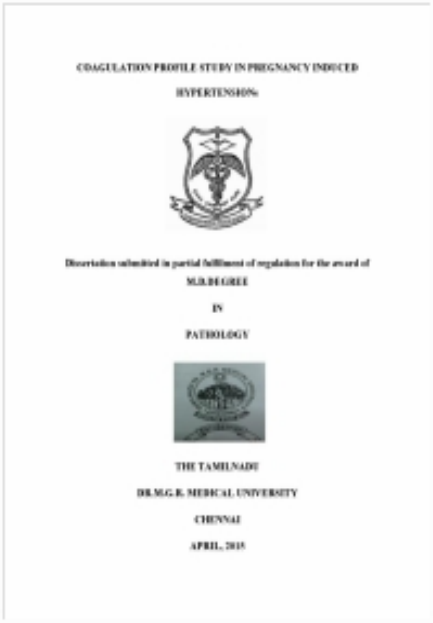

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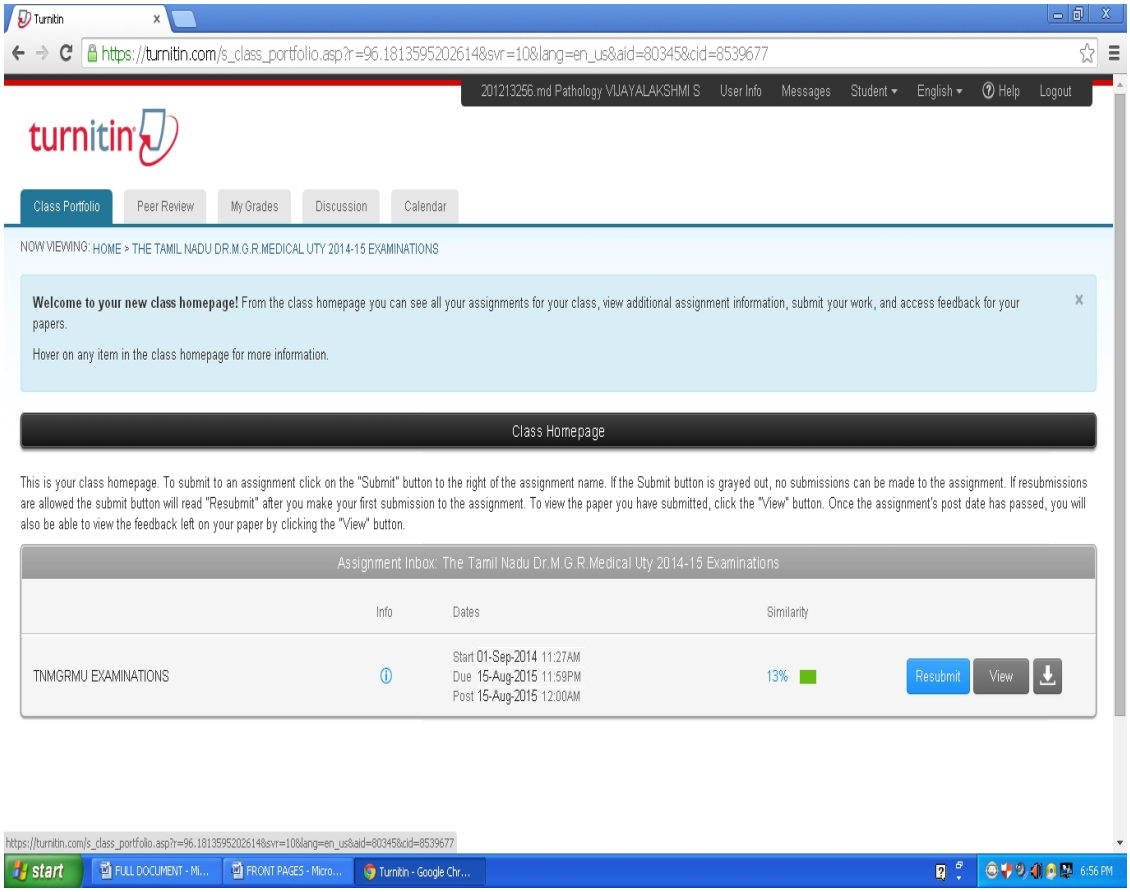
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ABBREVIATIONS

PIH	-	Pregnancy Induced Hypertension
PT	-	Prothrombin Time
APTT	-	Activated Partial Thromboplastin Time
BT	-	Bleeding Time
CT	-	Clotting Time
sFlt	-	Soluble fms-like tyrosine kinase.
INR	-	International Normalised Ratio
EDTA	-	Ethylene DiamineTetraacetic Acid
vWF	-	von Willebrand Factor
mpl receptor	-	Myeloproliferative leukemia virus receptor
nm	-	Nanometer
fl	-	femtolitre
DNA	-	Deoxyribonucleic acid

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ABSTRACT

AIM:

To study coagulation profile changes in pregnancy induced hypertension. Methods and Materials: Control group consists of 60 normotensive pregnant women compared with 30 cases of non-severe PIH and 30 cases of severe PIH. Coagulation parameters BT, CT, Platelet Count, PT and APTT were done for all cases. Observations: Patients with severe PIH patients showed low Platelet Count, prolonged BT, PT and APTT compared to normotensive pregnant women and non-severe PIH. No changes observed in CT. Summary and Conclusion: The changes in Coagulation Profile in severe PIH is helpful in assessing the Coagulation abnormalities at earlier stage. Changes observed in the coagulation parameters as the severity of PIH increases.

KEYWORDS:

Pregnancy Induced Hypertension, Bleeding Time, Clotting Time, Platelet Count, Prothrombin Time, Activated Partial Thromboplastin Time.

INTRODUCTION

Pregnancy induced hypertension is an elevated blood pressure that appears first time after five months of pregnancy. It is one of the most common cause of increased mortality and morbidity both in the mother and in the foetus.

Preeclampsia is a combination of elevated blood pressure, proteinuria and edema. Eclampsia is the presence of convulsions along with above three features of preeclampsia.

Normal pregnancy is a hypercoagulable state due to elevation of the most of the coagulation factors and reduced anticoagulant activity. In pregnancy induced hypertension, there is an accentuation of hypercoagulable state as a result of injury to the endothelium.

Coagulation profile studied in pregnancy induced hypertension are platelet counts, bleeding time, clotting time, prothrombin time and activated partial thromboplastin time. These parameters are helpful in assessing the severity of coagulation abnormalities in pregnancy induced hypertension at earlier stage, prior to the occurrence of complications like HELLP Syndrome, disseminated intravascular coagulation and cerebrovascular complications.

Aim of the study is to find out the changes that occur in the coagulation parameters in pregnancy induced hypertension.Then it is compared with normotensive pregnant women. This study may help in reducing the mortality and morbidity that are caused by the coagulation abnormalities of the pregnancy induced hypertension.

AIM OF THE STUDY

Aim of the study is to find out the changes that occur in the coagulation parameters in pregnancy induced hypertension as compared to that in normal pregnancy.

OBJECTIVES

1. To study the changes in platelet count, bleeding time, clotting time, prothrombin time and activated partial thromboplastin time in pregnancy induced hypertension.
2. To study the above parameters in normal pregnant women.
3. To compare the above parameters between normotensive pregnant women and women with pregnancy induced hypertension.
4. To correlate the above parameters with severity of pregnancy induced hypertension.

REVIEW OF LITERATURE

COAGULATION PROFILE STUDY IN PREGNANCY INDUCED HYPERTENSION

Hypertensive disorders complicate 5 to 10% of all pregnancies and it is one of the major causes of maternal and foetal mortality and morbidity. As per WHO (Khan and colleagues, 2006) Hypertension and its complications contribute to 16% of maternal deaths in developed countries. Erg and colleagues study in United States (2003) reported that 16% of maternal deaths are related to pregnancy related hypertension.

TERMINOLOGY AND CLASSIFICATION

Working Group NHBPEP – National High Blood Pressure Education Programme (2000) Classification of Hypertensive Disorders complicating Pregnancy.[1]

1. Gestational Hypertension or Pregnancy Induced Hypertension.[2],[3],[4]
2. Preeclampsia and eclampsia Syndrome.
3. Preeclampsia Syndrome superimposed on chronic hypertension.
4. Chronic hypertension.[5],[6]

PREGNANCY INDUCED HYPERTENSION

Defined as significant raise in Blood Pressure after 20 weeks of pregnancy in a woman previously recorded normal blood pressure to

above 140 mm Hg systolic and 90 mm Hg diastolic and it is called as severe if the systolic blood pressure is above 160 mm Hg and the diastolic blood pressure is more than 110 mmHg. Severity is determined by the presence or absence of certain factors. Presence of symptoms like Headache, Visual Disturbances, Upper abdominal Pain, Oliguria, Convulsion, Low platelet Count, Elevated serum enzymes and creatinine indicate severe pregnancy induced Hypertension. In the absence of abovementioned features it is called as non-severe.

PATHOPHYSIOLOGY OF PREGNANCY INDUCED HYPERTENSION

In 1939 Ernest introduced the concept that pathophysiology of pregnancy induced hypertension is impaired perfusion of the placenta. According to Oxford Group in 1991 and supported by Roberts there are two stages in the development of pregnancy induced hypertension. Stage one is reduced placental perfusion and the stage two is maternal endothelial cell activation.[7],[8]

In normal pregnancy cytotrophoblastic cells invade the decidua and myometrium. These cells replace the endothelium and media of the spiral arteries and as a result low resistance large diameter arterioles are formed. They become resistant to vasopressor agents and the perfusion of the placenta is increased.[9]

In PIH the incomplete endovascular trophoblastic invasion occurs only in the decidual vessels but not in the myometrial vessels and these vascular changeslead toendothelial damage, proliferation of myointimal cells, medial necrosis and lipid accumulation in myointimal cells and macrophages. This was referred as atherosis by Hertig (1945).Superimposed thrombosis leads to hypoperfusion, hypoxia and release of placental debris.

PATHOPHYSIOLOGICAL CHANGES IN PREGNANCY INDUCED HYPERTENSION

Hyperdynamic circulation is caused by increase in maternal cardiac output .The systemic vascular resistance is altered compared to normotensive pregnant women and there is hyperdynamic left ventricular function.[10]

Intravascular volume during normal pregnancy is increased whereas in PIH there is minimal increase or no increase in intravascular volume. This is because of generalised constriction of the venules.[11]

The limited blood volume mainly affects the plasma volume so that there is development of hemoconcentration.

There is loss of resistance to the angiotensin II and catacholamines.The most important complication affecting the coagulation system in PIH is HELLP syndrome which consists of Haemolytic anaemia, Elevated Liver enzymes and Low Platelet count.

MORPHOLOGICAL CHANGES IN PREGNANCY INDUCED HYPERTENSION

KIDNEY:

The characteristic lesion is glomerular endotheliosis which is well demonstrated by electron microscopy. There is deposition of osmophilic material between the basal membrane and the endothelial cells which leads to the narrowing of the capillary lumen and there is increase in the cytoplasm of endothelial cells and mesangial cells. There is no change in the epithelial cells or foot processes, no proliferation ofmesangial cells, and no alteration in the architecture of the renal medulla. The nature of the osmophilic deposits on immunofluorescent technique shows material that reacts with antibodies against fibrinogen and fibrin.[12],[13],[14],[15]

LIVER:

The same kind of material present in the kidney is also found in the liver. There are many areas of subcapsular haemorrhage. In the periphery of the lobules there is presence of fibrin thrombi and surrounding this thrombi are areas of haemorrhage and necrosis called asperiportal haemorrhagicnecrosis.[16],[17]

FACTORS RELEASED FROM THE PLACENTA IN PREGNANCY INDUCED HYPERTENSION

1. Oxidative stress[18],[19],[20]
2. Cytokines includeTumour necrosis factor2 and Interlukein -6

3. Insulin like growth factors
4. Heparin binding endothelial growth factor-like growth factor.
5. Endothelin
6. Arachidonic acid metabolites.
7. Angiotensin type II – type1 receptor autoantibody and angiogenic factors.[21]

Study conducted by Reem Mustafa[22] et al in the year 2012 reveals that the imbalance of proangiogenic and antiangiogenic factors is an important factor in the pathogenesis of pregnancy induced hypertension. There is increased expression of soluble fms –like tyrosine kinase.It is an antiangiogenic factor.It antagonizes vascular endothelial growth factor and placental growth factor. Soluble endoglin is a placenta derived coreceptor for transforming growth factor beta. It antagonises the effect of transforming growth factor beta which is an angiogengic factor. [23],[24],[25],[26],[27]

ENDOTHELIAL CELL ACTIVATION

As a result of damaged endothelial cells the amount of nitric oxide and prostacyclin production by the endothelium becomes less.[28],[29],[30],[31],[32],[33],[34],[35],[36]

For the pathogenesis of pregnancy induced hypertension, the activation and damage of endothelial cells is an important mechanism.It was a study conducted by J.Heimrath[37] et al in the year 2007.

ROLE OF ANGIOGENIC AND ANTIANGIOGENIC PROTEINS

By the time of 21 days of pregnancy placental vasculogenesis is established.Two antiangiogenic peptides involved in PIH are [38],[39]

1. Soluble Fms- like tyrosine kinase 1

Increased levelof this cause reduction of placental growth factor and vascular endothelial growth factor leading to dysfunction of endothelium.[40],[41]

2. Soluble endoglin

It inhibits Transforming Growth factor-beta isotopes.

COAGULATION CHANGES IN NORMAL PREGNANCY

1. Fibrinogen

Fibrinogenlevelin nonpregnant women ranges from 200 to 400 mg/dL. In pregnant women the level increases and can reach upto600mg/dL in the third trimester. [42],[43],[44]

2. Clotting factors VII, VIII, IX and X levels are increased and there is no change in factors II and XI.

3. Activated Partial Thromboplastin Time is shortened.

4. Protein C is unchanged and there is acquired activated protein C resistance.

5. Protein S levels are reduced.

6. Markers of thrombin production are elevated in pregnancy.

7. D-Dimer levels are high compared to non-pregnant level.

8. Fibrinolysis

It is suppressed and there is elevation of plasminogen activator inhibitor. Placenta produces plasminogen Activator inhibitor-1 and it is the main source of plasminogen activator inhibitor-2 which plays a main role in reduction in tissue plasminogen activator activity. Compared to non-pregnant level at normal term pregnancy the level of plasminogen activator inhibitor-2 is 25 times high.[45],[46],[47]

9. Platelets

As a result of increased consumption there is a moderate decrease in the platelet concentration as pregnancy advances. Regarding lifespan andfunction there is no change. Mean platelet size increases throughout the gestation. Due to accelerated production of platelets from the bone marrow platelet distribution width increases. Gestational thrombocytopenia is not a pathological condition and it the most common cause of thrombocytopenia during pregnancy. In pregnancy 5 to 8 per cent of women show low platelet count .There is no risk of bleeding even though there is platelet count as low as 1,00,000 per cubicmillimeter. Enhanced platelet activity compensates the low platelet count. Low platelet count may be due to the effect of dilutional thrombocytopenia. Greater numbers of younger platelets are present in the circulation. In the smear they appear large. A high level of thromboxaneA2 in pregnancy causes platelet aggregation.[48],[49],[50],[51]

Hence pregnancy is a hypercoagulable state because of the changes in the coagulation and fibrinolysis. Thromboplastic substances released at the time of delivery from the placenta stimulate clot formation. Physiological adaptations occurring during pregnancy are to help the mother from untoward bleeding complications during labour.[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64]

COAGULATON CHANGES IN PREGNANCY INDUCED HYPERTENSION

Reduction in the formation of vasodilator and antiplatelet agents such as prostacyclin and nitric oxide in association with increased levels of endothelin the endothelium becomes antithrombotic to prothrombotic.Downregulation of fibrinolytic system occurs.

Thrombocytopenia is due to

1. Reduction of platelet lifespan
2. Increased platelet consumption
3. Decreased prostacyclin synthesis
4. Immunological mechanisms.

Rahim[65] et al study in the year 2010 revealed that low platelet count was present in disseminated intravascular coagulation.

FahirElsirmohammed[66] et al study in the year 2013 revealed that the mean platelet volume and platelet distribution width were increased and the count of the platelet is reduced. Their study also proved that for

the assessment of pregnancy induced hypertension the platelet estimation is a rapid and simple cost effective method to diagnose the haematological changes.

Fitz Gerald [67] et al study in 1966 said that the estimation of prothrombin time, activated partial thromboplastin time and fibrinogen level are important in patients with pregnancy induced hypertension. In their study they found out in the presence of normal platelet count, there were minor changes in the prothrombin time, activated partial thromboplastin time and fibrinogen level.

S.Kawaguchi[68] et al study in year 2013 showed that increased D-Dimer levels during third trimester of pregnancy in patients with pregnancy induced hypertension.

Srivatsava[69] et al study in the year1995 revealed thatseverity of pregnancy induced hypertension can be assessed by reduction in antithrombinIIIlevel.

NORMAL HAEMOSTASIS

Depends upon three important factors such as

1. Platelets
2. Coagulation system
3. Vascular endothelium

PLATELETS

In 1841 Addison described as extremely minute granules. Recognised in 1882 by Bizzozero as cell structure having adhesive properties termed platelets and does not come under white blood cells or red blood cells. Osler and schaeter, in 1970 described the role in haemostasis and thrombosis. The bone marrow cell was called as megakaryocyte by Howell in 1890.James Homer Wright identified that platelets are produced from bone marrow precursor cell megakaryocyte in 1906.

They are discoid shaped cells and products of fragments of megakaryocyte cytoplasm.Interaction of platelets with coagulation system and vascular endothelium plays a major role in normal haemostasis.

DEVELOPMENT

During foetal life platelets are produced from the yolksac and the production of platelets is shifted later to the liver and then to the bonemarrow. Hematopoietic stem cells are found in the intraembryonic aorta and gonad mesonephros region.During the third month of foetal life stem cells migrate to the liver. By birth bonemarrow becomes the hematopoietic organ.[70]

STAGES OF DEVELOPMENT

Pleuripotent hematopoietic stem cell

↓

Common myeloid progenitor

↓

Colony forming unit erythroid megakaryocyte

↓

Burst forming unit megakaryocyte

↓

Megakaryoblast(stage-1)

↓

Megakaryocyte (stage II/III/IV)

↓

Platelet

Endomitosis is an important feature in megakaryocyte development in which DNA replication occurs without cell division. Through repeated cycles of DNA replication megakaryocytes become polyploid. They enter into anaphaseA and do not enter into anaphaseB. There is reduction in mitosis promoting factor or reduced expression of cyclin B and overexpression of cyclinD in the phase of maturing megakaryocytes. Absence of chromosomal passenger proteins AuroraB/Aim-1 and Survivin.[71]

Cytoplasmic maturation begins during endomitosis and formation of specific protein organelles and membrane systems. The internal membrane system in the mature megakaryocyte is referred as demarcation membrane system.There is formation of platelet territories within the cytoplasm. Fragmentation of cytoplasm produces platelets along demarcation membrane fracture lines between platelet territories. Young platelets contain ribonucleic acid and are called reticulate platelets. Large and beaded platelets are produced under stress are called as stress platelets.The time taken for the production of 1000 to 5000 platelets from one megakaryocyte is about ten days.

THROMBOPOIETIN

It is a glycoprotein hormone produced mainly from the parenchymal cells and sinusoidal endothelial cells of liver and proximal convoluted tubule cells of the kidney. It is also produced in minimal amount by skeletal muscle and stromal cells of the bone marrow. It binds to the mpl receptor present in the megakaryocyte and platelet.

Functions of thrombopoietin are

1. Proliferation and maturation of megakaryoblast
2. Regulate the development of megakaryocyte in all stages from the stem cell.
3. Increase in size and number of megakaryocytes so that the number of platelet production is also increased.

Other factors involved in thrombopoiesis are Cytokine stem cell factor,Granulocyte macrophage colony stimulating factor and Interleukins-3,6and11.

Once released from the bone marrow majority will be present in the circulation and 20% present in the spleen.There is no reserve in the bone marrow. The normal platelet count is $250x10^9$(Range150-$400x10^9$). Each platelet makes 14,000 drips through the blood stream in its life span of 7 to 10 days. In the circulation they exist in two forms,one is resting form and the other one is active form. Mean diameter of platelet is 1-2 µm and the mean cell volume is 5.8fl.[71],[72],[73]

STRUCTURE OF PLATELETS

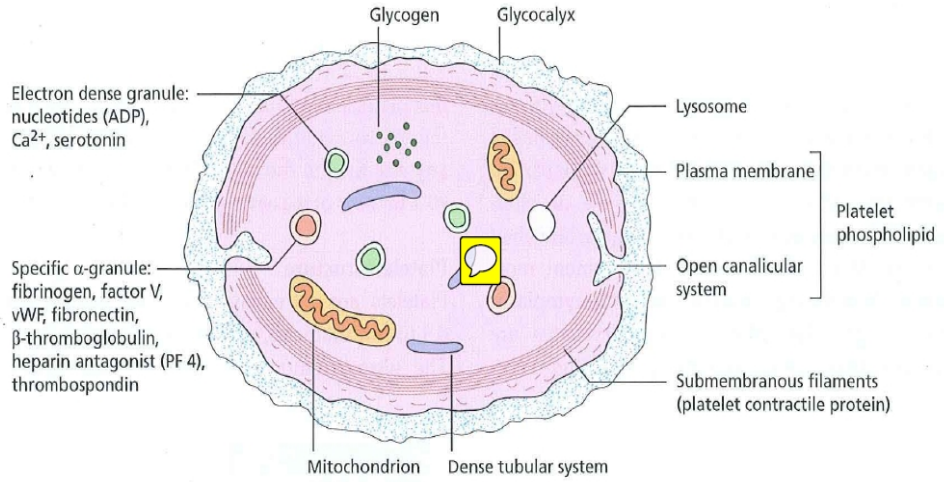
By ultrastructure three zones are studied

ZONE ONE – PERIPHERAL ZONE-It contains exterior coat,cell membrane and open canalicular system.

ZONE TWO – CYTOSKELETAN OR SOL-GEL ZONE - This consists of microfilaments, circumferential microtubules and dense tubular system.

ZONE THREE- ORGANELLE ZONE- This contains alpha granules, dense granules, mitochondria and lysosomes.

Ultra structure of platelets



EXTERIOR COAT

It contains glycoproteins, glycolipids,mucopolysaccharides and absorbed plasma proteins.Thickness of this coat is 15 to 20 nm. It has close contact with cellular and fluid component of the blood.It covers the plasma membrane and also the surface connected canalicular system. The interior contents pass through this coat into blood by endocytosis.

THE PLASMA MEMBRANE

Trilaminar membrane composed of proteins, lipids and carbohydrates. The content of bilayered lipid layer is mainly composed of phospholipids and the distribution is asymmetrical. Prostaglandins are produced from the phospholipids.It also controls the transport of sodium and calcium ions by the presence of pumps like sodium- and calcium-adenosine triphosphates.The presence of negatively charged phosphatidylserine in the inner leaflet controls the coagulation.

SURFACE CONNECTED SYSTEM

It is the modification of the plasma membrane over the surface. The functions of this system are storage for membrane glycoproteins such as GPIb-IX-V and GPIIb-IIIa, pathway for release of secretory granules when the platelets are activated, act as a barrier between blood and platelet and helpful for adhesion of platelets by spreading the membrane.[74],[75],[76],[77]

CYTOSKELETON(SOL-GEL ZONE)

DENSE TUBULAR SYSTEM

It is one of the sites for prostaglandin production. It is nothing but smooth endoplasmic reticulum of the megakaryocyte and in electron microscopy it appears as an amorphous electron dense material. It contains peroxidase, glucose-6 phosphatase, adenylatecyclase and calcium and magnesium activated adenine triphosphatase. [78]

MICRO FILAMENTS

They are binding proteins in which actin constitutes 20-30% of the total platelet protein and myosin constitutes 2-5% of the total platelet protein. They are responsible for platelet retraction/contraction and platelet shape. Under stimulation of platelets the actin monomers polymerize and fill the developing filopodia. Phosphorylation of myosin results in binding of myosin with actin and gives tension for filopodia.[79]

MICROTUBULES:

Disassembly and reassembly occur under platelet activation. It consists of two subunits which are not identical. Micro tubule coil lies just adjacent to the plasma membrane. It plays an important role in platelet formation from megakaryocytes and in maintaining the discoid shape of the platelet.

ORGANALLE ZONE:

Responsible for platelet storage and platelet release functions.

ALPHA GRANULES:

They are the predominate granules present in the platelet. Each platelet contains about 50-80 alpha granules. The size is 200-300nm.It contains Thrombospondin, von Willebrand factor, Multimerin, Fibrinogen, Fibronectin, Vitronectin and P-selectin which are responsible for platelet adhesion. P-selectin is transferred to the plasma membrane under the effect of platelet activation. The growth modulators present are platelet derived growth factor and transforming growth factor-β. The platelet specific proteins present are platelet factor 4 and β-thromboglobulin.

The two important coagulation proteins are fibrinogen and factor 5 and other coagulation factors are factor XI,protein S and plasminogen activator inhibitor-1. The granules are spherical in shape with outer membrane. The membrane consists of large electron dense region and

low electron dense zone. The platelet specific proteins are present in dense region. Adhesive proteins are present in low electron dense zone. Megekrayocyte produces β-thromboglobulin, platelet factor 4, thrombospondin and von Willebrand factor.

DENSE GRANULES

They are few in number and opaque, normally 3-8 per platelet. The size of the granule is 20-30nm.The content of the dense granules are high concentrations of serotonin, calcium, adenosine diphosphate and adenosine triphosphate .Granule membrane contains P-selectin and granulophysin.From the plasma high concentrations of serotonin is transferred to the granules through the plasma membrane. Serotonin is responsible for platelet coagulant activity, liver regeneration and vasospasm. Adenosinediphosphate and adenosine triphosphate are synthesized by megakaryocytes. The high concentration of adenosine diphosphate is an important mediator of platelet aggregation.

LYSOSOMES:

They play a major role in lysis of thrombi. It contains β-glucuronidase,β-galatctosidase,arylsulfatase,cathepsins and β-hexosaminidase. Under platelet stimulation these are released very slowly.

MITOCHONDRIA:

They are the site for respiratory chain and citric acid cycle. They are approximately 7 per platelet and smaller in size compared to other areas.

MICROPEROXISOMES:

They are the source of platelet activating factor and the size is about 90nm in diameter.

COATED VESICLES:

They transfer the contents of the plasma into the granules and their number is increased with the stimulation of adenosine diphosphate.Its size is about 70-90 nm in diameter.

PLATELET FUNCTION:

To maintain the normal haemostasis following damage to vascular system platelets play a main role in forming mechanical plugs. Both platelet adhesion and aggregation reactions are needed for the formation of haemostatic plug at the site of vascular injury.

PLATELET ADHESION:

Adhesion of platelets to the subendothelial collagen is a step wise reaction. The factors which are present in the subendothelial matrix are collagens, vonWillebrandfactor, fibronectin, thrombospondin-1,laminins and microfibrils.

Adhesive receptors present in the platelets are GPIb-V-IX,GPIIb-IIIa, GPIc-IIa,GPIa-IIa and vitronectin receptor. After vascular injury there is exposure of subendothelial matrix to the blood and blood components. The first reaction is formation ofcoating ofvWFmultimer at the exposed surface. After that the platelets with the help of GPIb-V-IX binds to vWF. Then rolling of platelet occurs.[80],[81],[82]

PLATELET ADHESION –FUNCTION OF GPIb-V-IX RECEPTOR:

It acts a link between platelets and subendothelial matrix by binding to von Willebrandfactor(vWF). It is a receptor for vWF.vWFdependent adhesion of platelet depends on the shear rate of the blood flow. Because of the high shear rate conformational changes occur in platelet receptor GPIb or in the Collagen typeI and collage type III helps in binding of vWF and platelets. Interaction of vWF with receptor causes rolling of platelets along the surface of vascular injury.

Bridging of cells to the subendothelial matrix occurs due to the rolling.Collagen plays a role in platelet adhesion.Subendothelial collagen, microfollicularcollagen typeIV acts as substrate for platelet adhesion and it functions as a platelet against.Collagen with the help of following three receptors making adhesion with platelets.They are GPIb-V-IX,GPIa-IIa and GPVI.

There is another mechanism of platelet adhesion with endothelial cell p-selectin which is present in alpha granules and weibel –palade bodies of endothelial cells. Exposure of p-selectin on the surface of the endothelium may promote platelet adhesion by binding to GP-Ibcomplex on platelets.[83]

Various other substrates capable of binding platelets are laminin, thrombospondin, fibronectin, and vitronectin.

In various inflammatory conditions the normal preventing mechanisms are altered and there is adhesion of platelets occur.Inflammation also induces the release of molecules that enhance adhesion of platelets. Leukocyte adhesion occurs in the inflammation which also induces platelet adhesion.Interaction of p-selectin of platelet and p-selectin of leukocyte occurs initially and then binding of fibrinogen to the leukocyte occurs.Platelet activating factor released by the platelets binds to the receptor known as platelet activating factor receptor which is present on leukocytes and later on binding of fibrinogen and factor x occurs. Adhesion also occurs between leukocytes and platelet junctional molecule-3 or GPIb.

SUBSTANCES PREVENTING PLATELET ADHESION TO ENDOTHELIUM

1. Nitric oxide

It is potent vasodilator synthesised from the endothelium by the action of endothelial nitric oxidesynthase. Both cyclic GMP-dependent and independent mechanisms play a role in nitric oxide induced inhibition of platelet adhesion and activation. Nitric oxidemay also inhibit leukocyte-dependent platelet adhesion to endothelium.

2. Prostacyclin

It is a prostaglandin derivative. It increases the activation of adenylatecyclase, thereby increasing the level of cyclic adenosine monophosphate, causing smooth muscle relaxation. It is a potent inhibitor of platelet aggregation.

3. Ecto-adenosine diphosphatase(CD39or ADPase)

It is present in the endothelial cell surface membrane. Adenosine diphosphate is a most potent stimulator of platelets. It is metabolised by this enzyme ADPase

4. Endothelial surface layer

It is called as glycocalyx lies between running blood and the endothelial membrane which is composed of glycoproteins and proteoglycans. This layer prevents the adhesion of platelets to the endothelium.

PLATELET SHAPE CHANGE:

In response to agonist's action on platelets shape change occurs. Agonists are von Willibrand factor, thromboxaneA2, thrombin, adhesion, epinephrine, serotonin, Adenosinediphosphate, thrombospondin, fibrinogen, vasopressin and immunecomplexes. Upon activation a change in shape from disc to sphere is observed as first event. Intracellular calcium level in platelets is elevated and the protein gelsolin is activated.As a result number of actin filaments in the platelet is increased.Swelling of membrane cytoskeleton occurs. Then incorporation of plasma membrane with open canalicular system develops. Polimerisation of actin leads to formation of lamillopodia and filopodia. Two proteins present in the platelets involved in the polymerisation of the actin are profilin and thymosin-β4. Peripheral microtubule coil compressed into the center of the platelet and surrounds the granules and organelles.Myosin light chain kinase causes activation of myosin and then interaction of actin and myosin occurs.

PLATELET SPREADING AND SURFACE INDUCED ACTIVATION

This is determined by the nature of the protein surface and the density of the protein.Activated platelets cause granule release and exposure of activated αIIbβ3receptors on the luminal surfaces of the platelets.This inturn recruit additional platelets.Lateral dissociations of

platelets developed by αIIbβ3receptors resulting in broad lamellopodia.Actin filament crosslinking protein filaminA form orgagonal network of actin filaments in lamellopodia.Calcium-dependent calpains also helps in spreading.

PLATELET CONTRACTION AND SECRETION

Contraction of actin and myosin occurs by changes in the cytoplasmic calcium concentration. Cacium-calmodulin complex formed by the rise in calcium concentration activate myosin light-chain kinase.The proteins involved in platelet granule plasma membrane fusion are core or integral proteins,they are known as soluble N-ethylmaleimide-sensitive factor attachment protein receptors along with accessory proteins.

Platelets Secretion (release reaction) of both granule types occurs soon after adhesion. Various agonists can bind platelet surface receptors and initiate an intracellular protein phosphorylation cascade ultimately leading to degranulation.

Platelet activation leads to the appearance of negatively charged phospholipids (particularly phosphatidylserine) on their surfaces. These phospholipids bind calcium and serve as critical nucleation sites for the assembly of complexes containing the various coagulation factors.

PLATELET AGGREGATION

Interaction of one platelet with another is a major function of platelets. Release of the contents of dense-bodies is especially important since calcium is required in the coagulation cascade and Adenosine diphosphate (ADP) is a potent activator of platelet aggregation. ADP also begets additional ADP release, amplifying the aggregation process. A configurational change in membrane GPIIb-IIIa and binding of fibrinogen molecules to GPIIb-IIIa receptors on adjacent platelets induces aggregation of platelets.[84],[85],[86],[87],[88],[89],[90]

COAGULATION SYSTEM

HISTORY OF COAGULATION

400 BC Hippocrates, the father of medicine covered the wound of a soldier with skin and observed that the bleeding was stopped. Once the skin is removed the bleeding started again. The cooling theory or blood coagulation was introduced by Aristotle and he found that cooling of blood occurs when the blood was removed from the body. No clotting occurs if fibres were removed.

In the year 1627,clots were identified in veins at body temperature. William Hewson noticed that air and lack of motion were necessary for beginning of clotting and demonstrated that the clot came from liquid portion of blood in the year 1770. Coagulation factors are assembled by scientist Paul Morawitz in 1905. He observed that in the

presence of calcium and thromboplastin, prothrombin was converted to thrombin which inturn converts fibrinogen into a fibrin clot.

In 1994 Paul Owren discovered the coagulation factor V and cofactor. Loeliger in 1952 called the cofactor as coagulation factor VII. Then Christmas factor or factor IX was identified. In the year 1957 factor X was introduced by Prower and Stuart.In 1953 factorXI was introduced into the coagulation system. In 1955 Ratnoff and Colopy discovered factor XII. In 1960 factorXII or fibrin stabilizing factor was demonstrated by Duckert. In 1965 prekallikrein or fletcher factor was discovered and in 1975 high molecular weight kininogen or fitzgerald factor was identified. By WilliamHewson the first whole blood clotting time was done in 1780 and he found that the blood of a healthy normal patient clotted in 7 minutes. In 1910 Koaguloviskosismeter was identified by Kottman.

COAGULATION SYSTEM

Plasma proteins in haemostasis can be divided into the following groups:

1. **Coagulation system-**

   Factor I ,II ,III, IV, V, VII, VIII ,IX, X, XI, XII, XIII, prekallikrein andhigh molecular weight kininogen.

2. **Fibrinolytic system-**

   Plasminogen,plasmin,tissue plasminogen activator,α2-antiplasmin,plasminogen activator inhibitor-1 and plasminogen activator inhibitor-2.

3. **Inhibitor system-**

Protein C,protein Sand antithrombin-III.

COAGULATION SYSTEM

Coagulation is a host defence system that maintains the integrity of the high pressure closed circulatory system. It is one of the important components in the normal haemostasis. It is a cascade of events in which inactive substances are activated ending in thrombin formation which in turn converts fibrinogen into fibrin monomers. Subsequently these monomers are polymerised in which platelets and other cells are encased and finally secondary haemostatic plug is formed.

Every step of coagulation cascade consists of activated coagulation factor that is enzyme, proenzyme form of coagulation factor that is a substrate and a reaction accelerator that is called as cofactor. All the above are combined with calcium ions on the phospholipid surface. Usually the coagulation occurs over the surface of activated platelets or endothelium.

Proenzymes called zymogens grouped into phospholipid bound zymogens and surface bound zymogens. Phospolipid bound zymogens are proteins which are vitamin k dependant.[91]

VITAMIN K DEPENDANT COAGULATION FACTORS

- Factor VII
- Factor X

- Factor II
- Factor IX
- Protein C

These proteins require vitamin K for their synthesis. They have 10-12 residues of γ-carboxyglutamic acid. This carboxylic reaction occurs by the help of membrane bound γ –carboxylase,which is located on endoplasmic reticulum. By this enzyme there is addition of γ-carboxyl group to the sialic acid residue group which are present in these zymogens. This carboxylation reaction enable these zymogens to bind to cell membrane and phospholipids followed by their activation there by helps in the formation of clot.

SURFACE BOUND ZYMOGENS:

They are-

- Factor XII
- Prekallikrein
- Factor XI

They are also called contact factors because factor XII autoactivates the intrinsic pathway of coagulation when it is exposed to thrombogenic surfaces. This phenomenon of autoactivation of factor XII is used in the laboratory test Activated Partial Thromboplastin Time(APTT).

COFACTORS:

They are also called as reaction accelerator. They are

- High molecular weight kininogen
- Factor VIII
- Factor V
- Fibrinogen
- Protein S

They act as a receptor for coagulation proteins. For example factor VIIIa acts as a receptor for factor IXa and factor Va is a receptor for factor Xa and high molecular weight kininogen functions as receptor for prekallikrein. These cofactors help in the activation of coagulation cascade. They also function as substrates of enzymes in coagulation events.

COAGULATION SYSTEM

COAGULATION:

There are number of proteins thatparticipate in normal coagulation finally leading to form fibrin clot. As per international system of nomenclature the coagulation factors are designated by Roman numerals from I to XIII. [92]

BLOOD COAGULATION FACTORS:

FACTOR	SYNONYM	ACTIVE FORM
I	Fibrinogen	Fibrin subunit
II	Prothrombin	Serine protease
III	Tissue factor, thromboplastin	Receptor/cofactor
IV	Calcium	
V	Labile factor,proaccelerin	Cofactor
VI	F VI has been determined to be activated form of FV and the term FVI is no longer used.	Serine protease
VII	Stable factor	
VIII	Antihaemophilic factor or globulin	Cofactor
IX	Christmas factor, Plasma thromboplastin components	Serine protease
X	Stuart-Prower factor	Serine protease
XI	Plasma thromboplastin antecedent	Serine protease
XII	Hageman factor	Serine protease
XIII	Fibrin stabilising factor, Lakilorand factor	Transglutaminase
Fletcher factor	Prekallikrein	Serine protease
Fitzgerald factor	High molecular weight kininogen	Cofactor

FIBRINOGEN:

It is a soluble glycoprotein synthesised from liver hepatocytes. Its level is highest among the coagulation proteins, ranges from 200-400milligram/dL in which 75% are present in the plasma and 25% are distributed in the lymph and interstitium. Molecular weight is 340 kilodaltons.

It is made up of 6 polypeptide chains. Two Aα chains, two Bβ chains and two γ chains are linked by disulphide bonds. There are two domains, domain E and domain D. Domain E is formed by amino terminal of all chains which participates in the formation of cross linking of chains. D domain is formed by carboxy terminal regions of Bβ and γ chains which is meant for protein- protein interactions. In the α and β chains there is a small peptide sequence which prevents the formation of fibrin polymers. Normal half-life is 3-5 days.

In the coagulation process formation of fibrin from fibrinogen takes place in various stages. The N terminals of the fibrinogen α and β chains are to form protofibrils which inturn associate latter to form fibrin fibres. The above said reaction is catalysed by thrombin. The fibrin strands are cross linked by factor XIII to form a clot. Factor XIIa stabilises fibrin further by incorporation of the fibrinolysis inhibitors alpha- 2- antiplasmin and thrombin activatable fibironlysis inhibitor,

procarboxypeptidase and binding to several adhesive proteins of various cells.

Both the activation of factor XIII by thrombin and plasminogen activator are catalysed by fibrin. Fibrin binds the activated coagulation factor Xa and thrombin and entraps them in the network of fibres. Thus functioning as a temporary inhibitor of these enzymes it can form bridges between platelets by binding to their GPIIb/IIIa surface membrane proteins.

PROTHROMBIN:

It is a single polypeptide glycoprotein produced from the liver having 579 amino acids with a molecular weight of 72,000daltons. The gene for prothrombin and thrombin is located on chromosome number 11. Normal concentration of prothrombin in the blood is approximately 100µg/ml. Half-life of prothrombin is 3 days.

After synthesis it undergoes post translational modification by vitamin K dependant reaction. In this reaction glutamic acid in the 10^{th} position is replaced by γ carboxy glutamic acid, it is called as γ carboxylation reaction.

Prothrombin is converted into thrombin by the action of prothrombinase complex. In this complex factor Xa activity is greatly enhanced by binding to activated factor V and calcium. Prothrombin is first converted into meizothrombin and then to α thrombin.

α thrombin is a potent activator of platelet and induces the release of contents of both α and dense granules. From the α granules many adhesive and procoagulant factors are released and from the dense granules adenosine diphosphate is released. α thrombin also induces the exposure of anionic surface of platelets. It cleaves the fibirinogen into fibrinopeptide A and fibrinopeptide B. It activates factor XI to XIa, factor VII to VIIa, factor V to Va and factor XIII to XIIIa. By combining with thrombomodulin it activates protein C. The activated protein C inactivates factor Va and VIIIa. A serine protease inhibitor antithrombin III blocks the action of thrombin.

Meizothrombin is a potent vasoconstrictor and activates factor XI and factor V and also augments α thrombin formation by activating factor XII.

Thrombin activatable fibrinolysis inhibitor:

It is otherwise known as plasma carboxypeptidase B, synthesised by the liver. It circulates in the plasma as a plasminogen bound zymogen. It is activated bythrombin/thrombomodulin complex. It reduces the fibrinolytic activity by removing the binding site for plasminogen. [93]

TISSUE FACTOR:

Tissue factor, also called platelet tissue factor, factor III, thromboplastin, or CD142 is a protein present in subendothelial distribution in all tissues and in high concentration in brain, placenta and

lungs and also present in leukocytes . It is a non-enzymatic cofactor for factor VIIa in the extrinsic tenase complex. It has got a high affinity receptor for factor VII. Gene for this is located on chromosome 1p21-22. It is a single chain glycoprotein.

Tissue factor can bind either factor VII or factor VIIa in the presence of calcium. This extrinsic tenase complex activates factor IX and X thereby extrinsic pathway of coagulation is initiated.

FACTOR V:

It is otherwise known as proaccelerin or labile factor. It is a coagulation protein synthesised from the liver and in the platelets as a large single chain glycoprotein. In the platelets it is presented in the α granules that constitutes 25% of the total factor V. The average plasma concentration is 20 nmol/L. Its molecular weight is 330 kilodaltons. Gene for this factor is present on chromosome-1q23. In contrast to other factors it is not enzymatically active and it acts as a cofactor. Plasma half-life is 12 hours.

It binds to activated platelets. α thrombin cleaves the single chain molecule into two chains, one is called light and the other one is called heavy. They are non-covalently bound to each other by calcium. Factor Xa cleaves factor V and produces active factor Va. Compared to α thrombin the effect of cleavage of factor Xa on factor V is less efficient.

Other factors like platelet calpain, cathepsin G, and human neutrophil elastase will also activate factor V partially.

It forms prothrombinase complex and stabilises the complex and helps in inactivation of prothrombin. On the cell membrane prothrombin is converted into thrombin with the help of activated factor X and activated factor V. In this reaction factor Va acts as a cofactor for factor Xa. It helps to anchor the factor Xa on the membrane surface of the platelets.

Thrombomodulin combines with thrombin and activates protein C. Protein C when it gets activated causes degradation of factor Va, thereby inhibiting the coagulation.

Lack of factor V in factor V Leiden mutation clotting will not occur. It is a very rare inherited coagulopathy.

FACTOR VII:

The gene for factor VII is located on chromosome 13. It is a single chain zymogen of a molecular weight of 50,000 daltons consists of 406 amino acids.It is synthesised mainly in the liver. It is also called as proconvertin with the plasma concentration 10 nmol/L. It binds to the membrane cofactor, tissue factor and helps in initiation of extrinsic pathway of coagulation. Among the coagulation factors it has very short half-life of about 3-6 hours.

Activation of factor VII to factor VIIa is occurred by α thrombin factor IXa, factor Xa, autoactivation of factor VIIa and factor XIIa. After activation single chain is cleaved into light and heavy chain.

Tissue factor is found on the outside of blood vessels. It is normally not exposed to the bloodstream. Upon vessel injury, tissue factor is exposed to the blood and circulating factor VII. Factor VII combines with integral membrane protein tissue factor to form extrinsic tenase complex. The extrinsic tenase complex contains activated factor VIIa, tissue factor, membrane surface and calcium which is extrinsic to the plasma environment. This complex activates factor X into Xa and factor IX into IXa.

FACTOR VIII:

FVIII is a non-enzymatic glycoprotein procofactor, synthesized and released into the bloodstream by the vascular, glomerular, and tubular endotheliumand sinusoidal cells of the liver. The gene that codes for FVIII is located on the long arm of the chromosome X. It is present in the plasma in combination with multimeric protein von Willebrand factor. This combination with vWF acts to regulate the plasma concentration and stabilisation of factor VIII. Its molecular weight is 2,80,000 daltons. It is secreted as two-chain heterodimers. It has copper ion binding site A domain, which is important for protein function. It also contains binding sites for vWF, anionic phospholipids, factor IXa and factor X.

α thrombin activates factor VIII into factor VIIIa. After activation it binds to factor IXa to form calcium and membrane dependant complex called as the intrinsic tenase complex. This complex activates factor Xa.

VON WILLEBRAND FACTOR:

vWF is a large multimeric glycoprotein present in blood plasma and produced from the Weibel-Palade bodies of endothelium, α-granules of platelets, and subendothelial connective tissue. It is synthesized as prepro molecule which undergoes extensive post translational modification to form mature vWF protein. The vWF gene is located on chromosome 12. Average plasma concentration is 10 µg/ml. Its level is increased with pregnancy, surgical trauma and stress. Individuals with type O blood group have lower level of vWF than type A,B, or AB blood groups.

The vWF monomer contains 2050 amino acids.The domains which are present in the vWF factor are D,C1,A1,A3 and cysteine knot domain. D domain has got binding site for factor VIII whereas C1 binding domain binds to platelet receptor GPIIb-IIIa. The A1 domain binds to platelet GPIb-receptor, heparin and collagen. The A3 domain binds to collagen.

Factor VIII is stabilised by vWF .It undergoes rapid degradation when it is not bound to vWF and half-life is prolonged when it is bound to vWF. Factor VIII is released from vWF by the action of thrombin.

vWF binds to platelet GPIb when it forms a complex with GPIX and GPV, thereby promoting platelet aggregation and adhesion. vWF binds to other platelet receptors when they are activated and also binds to collagen. vWFmutimers produced by the endothelial cells are large and they bind to and agglutinate platelets in the presence of high shear stress.

FACTOR IX:

It is also called as Christmas factor or hemophilia B factor or plasma thromboplastin component.

It is a glycoprotein consists of 415 aminoacids produced as zymogen in the liver. Factor IX gene is located on the chromosome X near factor VIII gene. It is a vitamin K dependent coagulation factor which undergoes gamma carboxylation in the presence of vitamin K.

It is cleaved by factor XIa or factor VIIa to produce two chains which are linked by a disulfide bridge. This cleavage occurs in two stages, the 1^{st} stage forms factor IXα and then the 2^{nd} stage forms IXa. It forms intrinsic tenase complex with its cofactor VIIIa, calcium and platelet membrane surface. This complex activates factor X to Xa.

DOMAINS:

Factor IX contains four protein domains. They are the Gla domain, two random copies of the EGF domain and a C terminal trypsin like peptidase domain.

Gla domain is for calcium binding, the EGF domain for tissue factor binding and platelet binding sites. The C-terminal trypsin like peptidase is for catalytic cleavage. The intrinsic tenase complex is more efficient in activation of factor X to factor Xa than extrinsic tenase complex. Factor IX is inhibited by antithrombin III.

FACTOR X (STUART- PROWER FACTOR):

It is also known as prothrombin, thrombokinase. It is a Vitamin K dependant glycoprotein produced from the liver. It is a serine endopeptidase. Its molecular weight is 59,000 Daltons. Plasma concentration is 170 nmol per litre.It contains two chains linked by disulfide bond. Its half-life is 40-45 hours.

` Activation of factor X is by extrinsic tenase complex and intrinsic tenase complex. Factor Xa cleaves prothrombin in two places, produces active thrombin. This occurs after the formation of prothrombinase complex.Factor Xa is activated by protein Z dependant protease inhibitor.

FACTOR XI:

It is the member of contact pathway.It is also called as Plasma thromboplastin antecedant.It is a Zymogen form of factor XIa, a serine protease. Factor XI is encoded by the FXI gene. Its average concentration is 30nmol/L.It contains 607 aminoacids and circulates as homodimer. Plasma half-life is 52 hours. Its gene is located on chromosome number 4. It is present in plasma and platelets. It has 4 apple domains, apple 1 to

apple 4. In the circulation it forms complex with HMWK. Apple 1 domain binds with anionic surfaces and α thrombin and prothrombin. The apple 2 and apple 3 both bind to factor IX.

Factor XI is activated into factor XIa by factor XIIa, thrombin and factor XIa itself. Factor XIa activates factor Xa by cleaving peptide bonds. Factor XIa is inhibited by protein Z dependant protease inhibitor.

FACTOR XII

It is a plasma protein involved in blood coagulation, also named as Hageman factor. It is a zymogen precursor of factor XIIa. Average normal concentration in the plasma is 40 microgram per ml. In post-menopausal women with hormonal replacement therapy and in pregnant women the level of factor XII is increased. Structurally it consists of 596 amino acids in which a heavy chain and a light chain bound by disulfide bond. Its molecular weight is 18,000 Daltons. At the tip of long arm of chromosome 5 the gene for factor XII is present. It initiates coagulation on contact with thrombogenic surface and hence it is also called as contact factor.

Factor XII deficiency is not associated with bleeding tendency and hence its role in haemostasis is not clear. There are some studies in which mice with factor XII deficiency are protected from arterial thrombosis. Factor XII initiates autoactivation when it is exposed to

negatively charged surfaces like glass, kaolin and interaction with hydrophobic surfaces.

In our body it is usually activated by a cell membrane associated proteinase. Factor XII, prekallikrein and high molecular weight kininogen form a complex on anionic phospholipids of the cell membrane.This is the starting point of intrinsic pathway of coagulation. The prekallikrein is divided to form the enzyme kallikrein. This in turn activates factor XII. In addition to this activation, plasmin also activates factor XII and the factor XII is cleaved to form alpha factor XIIa. This cleavage causes exposure of the active site of factor XIIa and factor XIIa can bind with negatively charged surfaces to activate factor XI and prekallikrein.

Factor XIIa activates factor XI and prekallikrein. It also activates the complement system and down regulates Fc receptor on the macrophages and monocytes to release interleukin 1 and interleukin 6. It stimulates neutrophils.Hence there is a link between inflammation and coagulation.

Factor XII deficiency is a very rare autosomal recessive condition in which there is no abnormality observed in the haemostatic system.

FACTOR XIII OR FIBRIN STABILIZING FACTOR:

It is also known as Laki-Lorandfactor in 1948 by scientist. It functions as transglutaminase. It circulates as a heterotetramer composed

of two A-chains and two B-chains. Gene for A-chains situated on chromosome 6 and for B-chains on chromosome 1.

Bone marrow is the main site of synthesis for the plasma factor XIII-A chain. Intracellular factor XIII is present in platelets, megakaryocytes and monocytes. It is a heterodimer which has two catalyticsubunits,A subunithas enzymatic activity and B subunit act as a carrier.

Factor XIII is converted to factor XIIIa in the presence of cofactor calcium. Factor XIII uses cysteine for catalysis. Fibrinogen is converted into fibrin by thrombin, then activated factor XIIIa acts on fibrin to form an insoluble clot.

Substrates for factor XIII include fibrin, fibrinectin, α_2 plasmin inhibitor, collagen, vitronectin, vWF, actin, myosin, factor V and thrombospondin.

PROTEIN C:

It is also called as antiprothrombin II A and blood coagulation factor XIV.It is a Zymogen form of activated protein C. Its half-life is 8 to 10 hours. Gene is located on chromosome Z. Synthesised in the liver as prepro sequence of having 42aminoacids which is a single chain polypeptide.

Light and heavy chains are linked by disulfide link. Protein C is activated when it binds to thrombin in the presence of thrombomodulin and endothelial protein C receptors.

PREKALLIKREIN (FLETCHER FACTOR):

In 1965 Hathaway described this factor and in the year 1973 this factor is named as “Fletcher factor’’. It is a serine protease precursor of kallikrein. In combination with high molecular weight kininogen Kallikrein activates kinins. Activated factor XII is needed for production of kallikrein from prekallikrein.

Plasma prekallikrein is a glycoprotein, synthesised in the liver and secreted into the blood as a single polypeptide chain.Gene is located on chromosome 4 close to factor IX gene. Normal concentration in the plasma is 486 nmol/L. 3/4 of the total concentration forms complex with high molecular weight kininogen and 1/4 of it is free in the plasma. It participates in the surface dependant activation of coagulation, fibrinolysis, kinine generation and inflammation.

Prekallikrein is activated by two ways. In one way by β-factor XII without an anionic surface and the other one is in combination with activated factor XII and with the help of cofactor high molecular weight kininogen on the anionic surface. In both ways cleavage occurs between arginine and leucin. This reaction also occurs when prekallikrein is bound to high molecular weight kininogen without the help of factor XIIa.

Prekallikrein consists of a heavy chain which is for surface dependant procoagulant activity and the light chain containing active site or catalytic domain. Plasma prekallikrein deficiency causes prolonged activated partial thromboplastin time in patients. It acts as a link between coagulation and fibrinolytic system.

KALLIKREINS:

Plasma kallikrein produces kinins from kininogens for regulation of blood pressure and activation of inflammation. It helps in the formation of plasmin from plasminogen. Kallikrein with factor high molecular weight kininogen activates factor XII to factor XIIa and proteolysis of factor XIIa to β- factor XII and this reaction occurs with anionic surface. Bradykinin is produced from high molecular weight kininogen by the action of kallikrein. Bradykinin induces the endothelial cell for the formation of prostacyclin from arachidonic acid metabolites which causes dilatation of vascular system and reduction of blood pressure. Kallikrein activates neutrophils and stimulates elastase release. C1 inhibitor, α macrogloblin and antithrombin III regulates the activity of kallikrein.

HIGH MOLECULAR WEIGHT KININOGEN:

It is a circulatory protein which participates in the initiation of blood clotting, generation of bradykinin and kinins. It is an alpha globulin with 6 functional domains. It is a single chain polypeptide containing 626 amino acids. Heavy chain contains 1,2 and 3 domains and

the light chain contains 5 and 6 domains whereas the domain 4 links the light and heavy chains.

FUNCTIONS OF DOMAINS:

Domain 1	It has low affinity calcium binding capacity.
Domain 2	Inhibits cysteine protease such as cathepsin.
Domain 3	Inhibits cysteine protease and it will have platelet and endothelial cell binding.
Domain 4	It is for bradykinin production and it also inhibits α-thrombin.
Domain 5	It binds to heparin and cell binding and also binds to negatively charged surfaces.
Domain 6	It has prekallikrein and factor XI binding capacity.

MECHANISM OF BLOOD COAGULATION:

Blood coagulation involves a cascade of events in which proteolysis of circulating precursor proteins ends in the generation of thrombin. This thrombin converts fibrinogen which is a soluble plasma protein into insoluble fibrin. Platelets are entrapped in the fibrin mesh at the site of vascular injury and platelet aggregation occurs into the fibrin mesh and then finally the unstable platelet plugs are converted into stable haemostatic plugs. There are many coagulation factors which are involved in this coagulation cascade.

INITIATION OF COAGULATION:

As a result of vascular injury, membrane bound tissue factor is exposed. Tissue factor interacts with active form of factor VIIa. After that activation of both factor IX and factor X occurs by the activation of complex which consists of factor VIIa and tissue factor. The activated Xa forms small amount of thrombin from prothrombin. This reaction initiates coagulation.

AMPLIFICATION:

The small amount of thrombin formed in the initial stage of coagulation leads to amplification of coagulation system. In this phase intrinsic tenase complex is formed by factor IXa and VIIIa in the presence of calcium over the phospolipid surface. This process activates factor Xa which then in combination with Va, phospolipid and calcium forms the prothrombinase complex and results in the explosive generation of thrombin which acts on fibrinogen to form the fibrin clot.

COAGULATION PATHWAYS:

It is divided into extrinsic, intrinsic and common pathways.

INTRINSIC PATHWAY:

Contact of plasma with negatively charged surface is provided by the subendothelium of a damaged vessel. Following this contact initiation of intrinsic pathway occurs by conformational change in factor XII which is converted into factor XIIa.

This active form of XIIa converts prekallikrein to kallikrein and inactive factor IX to factor IXa. In the presence of high molecular weight kininogen, Factor XIa cleaves factor IX to give factor IXa. For this reaction calcium and phospholipid are needed. Factor X is converted into Xa by means of factor IXa complexes with factor VIII, phospholipid and calcium. Factor VIII is activated by thrombin and also by factor Xa. Factor VIII acts as a cofactor and accelerates the reaction.

EXTRINSIC PATHWAY:

In this pathway as a result of tissue injury tissue factor is released. This tissue factor complex with factor VII and in the presence of calcium leads to activation of factor X and factor IX. Factor Xa and thrombin converts the single chain form of factor VII to two chain form which has got enzymatic activity. This reciprocal activation of factor VII leads to auto amplification of the reaction.

COMMON PATHWAY:

This pathway starts with activation of factor X. Both intrinsic and extrinsic pathway generates factor Xa. This activated form of factor X complexes with factor V, phospholipid and calcium. This complex converts prothrombin to thrombin. Either thrombin or factor Xa activates factor V which functions as a cofactor.

Thrombin acts on fibrinogen which contains α and β chains to remove fibrinopeptides A and B. Thereby the fibrin monomer is formed.

Polymerisation of fibrin monomers occurs spontaneously by the formation of non-covalent bonds which are end-to-end and side-to-side. In this way the fibrin polymer is formed. Factor XIIIa which is formed from inactive factor XIII by the action of thrombin. It mediates the formation of covalent bonds between adjacent polypeptide chains in the presence of calcium. This cross linking of fibrin monomers forms stable clot.

FIBRINOLYTIC SYSTEM:

PLASMINOGEN:

It is synthesised in the liver and has a molecular weight of 92 Kilo daltons. It is composed of a single chain and there are two forms Glu-plasminogen which is larger having N-terminal glutamic acid and other form is Lys-plasminogen. Lys-plasminogen is formed in the circulation by plasmin cleavage and it rapidly binds to fibrin via lysin binding sites. When plasminogen is activated it is converted into active two chain plasmin with a serine active site on heavy chain that is connected to light chain by disulphide bonds.

Plasmin causes proteolysis of fibrinogen and fibrin. Plasmin also degrades other proteins including factor VIII, factor V, vWFand others. The cleavage of fibrinogen and fibrin leads to the formation of fibrin degradation products. Fibrinogen on degradation first gives largest

fragment X. Fragment X gives rise to fragments Y and D. Fragment Y is further proteolysed to give rise to a second fragment D and fragment E.

TISSUE PLASMINOGEN ACTIVATOR:

It is a physiological activator of plasminogen synthesised in endothelial cells which has got high affinity for plasminogen. Its molecular weight is 68,000 Daltons. In the circulation it usually complexes with its inhibitor plasminogen activator inhibitor-1. During the process of coagulation this complex is separated and free tissue plasminogen activator combines with fibrin so that its activity is enhanced. Compared to single chain form, two chain form has got three fold higher activity.

UROKINASE PLASMINOGEN ACTIVATOR:

It is found in the kidney, urine and fibroblast-like cells and it is a single chain zymogen. It also activates plasminogen.

PLASMINOGEN ACTIVATOR INHIBITOR-1:

Synthesised by the endothelial cells and acts as a physiological inhibitor of tissue plasminogen activator. Plasminogen activator inhibitor-2 which is found in plasma and plasminogen activator inhibitor-3 also inhibit tissue plasminogen activator.

ANTIPLASMIN:

It is a physiological inhibitor of plasmin synthesised by the liver with molecular weight of 58,000 Daltons. It inhibits plasminogen binding

to fibrin and inhibits the proteolytic activity of plasmin. By the action of factor XIIIa it binds to fibrin in a covalent manner. By binding to fibrin antiplasmin competitively inhibits the binding of plasminogen to fibrin.

ENDOTHELIUM:

Normal vascular endothelium is one cell thick, separating the blood and vascular smooth muscle. It lines the interior surface of the blood vessels forming an interface between circulating blood and the rest of the vessel wall.

Endothelial cells are exposed to shear stress of the blood and the interaction between the cells and the vascular wall. It regulates the fluidity of blood through thrombo resistance and profibrinolytic potential. It regulates vascular permeability and fragility. It plays a major role in maintaining the lumen patency in the vascular system. Thrombo regulatory compounds are produced from endothelial cells.

In thrombus formation these compounds control platelet and vascular reactivity. They are eicosanoids, nitric oxide,endothelin and CD39/ENTPDI (ecto-nucleoside triphosphate diphosphohydrolase).

EICOSANOIDS

They are also called prostaglandins. They are produced from the essential fatty acids in diet. The main prostaglandin from the endothelium is prostacyclin (PGI2). Biosynthesis of PGI2 occurs by two methods. In rapid method agonists activate the phospholipase C.Increased

intracellular calcium brings the phospholipase A into the endoplasmic reticulum. It produces vascular relaxation, cytokine production and it blocks platelet reactivity.

Seventransmembrane G-protein coupled receptor that couples with adenyl cyclase which is present in platelet is type I prostaglandin receptor .This receptor activates protein kinaseA which inturn inhibit platelet activation and platelet recruitment.[94],[95]

NITRIC OXIDE:

It is a gas produced from vascular endothelial cells when vasodilators binds to the receptors over the endothelial cell membrane. It is short bind substance. It blocks the agonists induced platelet reactivity. It increases the cyclic guanosine monophosphate by acting on guanylatecyclase and inturn produces vascular relaxation and inhibition of platelet function. It reduces the expression of P-selectin on the platelets and inhibit the conformational changes in β2 integrin protein IIb-IIIa which is required for fibrinogen cross binding.[96],[97],[98],[99]

ENDOTHELIN:

It is a polypeptide regulating vascular tone by binding to a G protein coupled receptor on the cells of smooth muscle.It is produced from the precursor preproendothelin I by the converting enzyme into endothelin-I.Binding with receptor increases the calcium in the cytoplasm resulting in vasoconstriction.

ENDOTHELIAL CELL CD39/ENTPDI (ecto-nucleoside triphosphate diphosphohydrolase)

It is present in endothelial cells and leukocytes .It prevents further platelet activation and recruitment by metabolising adenosine diphosphate in the platelets. It has a good therapeutic application.

LATE THROMBO REGULATING SUBSTANCES:

They prevent excessive thrombin production. They also promote lysis of thrombi in the blood vessels. Anti-thrombin inhibits thrombin and factor Xa in the circulation.

It acts as natural anticoagulant. Heparin proteoglycans from endothelium play as cofactors for antithrombin. Tissue factor pathway inhibitor inhibits tissue factor and factor VIIIa complex. Direct anticoagulant effect on thrombin is mediated by thrombomodulin and protein C system. Endothelial cells control the formation of plasmin from plasminogen and also synthesise and secrete components of fibrinolytic system.Thromboregulatory system maintains the fluidity of the blood by interaction of blood cells and cells in the endothelium.

ROLE OF ENDOTHELIUM IN REGULATING CELL CIRCULATING FUNCTION

Cell-cell adhesion is dependent on interaction of cell adhesion molecules. P-selectin is present in platelets and in the weibel-palade bodies of endothelial cells. They are glycoproteins upon activation of

endotheleial cells they are expressed on the cell surface and binds to the counter receptors on circulating platelets and neutrophils.

Cytokines such as tumor necrosis factor α and γ, Interleukin-I and Interleukin-4 act on endothelial cells and make the cells proadhesive. Thus the endothelium regulates the migration of platelets, leukocytes and monocytes.

INHIBITORS OF COAGULATION:

Tissue factor pathway inhibitor (TFPI):

It is synthesized by micro vascular endothelial cells, monocytes and macrophages. Mostly they are bound to lipoproteins in the circulation. The free form is most active compared to bound form.

Tissue factor pathway inhibitorcontains three kunitz type protease inhibitor domains. The second kunitz domain inhibits the factor Xa. This action is needed for the action of first kunitz domain to inhibit factor VIIa/ tissue factor complex. The third kunitz domain binds to endothelial cell glycosaminoglycans and released by heparin.

ANTITHROMBIN:

It is the most important physiological serine protease inhibitor otherwise known as serpins. It is a single chain glycoprotein synthesized in the liver. It acts as a suicide substrate for their target protease through a surface exposed structure termed as reactive site loop.Anti-thrombin inhibits activated factor IX, activated factor X, activated factor XII and

thrombin. Heparin like substances enhances the anti-thrombin activity. It is a serine protease cofactor III.

ACTIVATED PROTEIN C:

It causes inactivation of factor Va and VIIIa by irreversible proteolysis. Protein C also enhances the fibrinolysis.

COFACTORS FOR ACTIVATED PROTEIN C:

Protein S:

It acts as a cofactor for activated protein C.

Factor V:

It enhances the action of activated protein C against factor S. It acts synergistically with factor V for the above reaction. High density lipoproteins and glycosphingolipids also act as cofactors for activated protein C.

TISSUE FACTOR PATHWAY INHIBITOR

It forms quaternary complex with factor VIIa, Tisssue factor and Factor Xa and causes neutralisation. It is a powerful inhibitor of FVIIa-tissue factor complex and it is serine protease inhibitor of Kunitz-type.

SCREENING TESTS FOR HEMOSTASIS

TESTS TO ASSESS THE PLATELET FUNCTION

- Bleeding time
- Platelet count
- Platelet function analyser-100and Platelet aggregation studies

BLEEDIND TIME:

By doing bleeding time,the function of the platelets are assessed and also the vascular components.So it is a measure of primary haemostasis.It is time taken for bleeding to stop after the puncture is produced on the skin surface allowing the free flow of blood

Increased bleeding time indicates impairment of platelet function or impaired contracture of the vasculature or both.

Methods for testing the bleeding time are

1. IVY'S METHOD
2. DUKE'S METHOD
3. TEMPLATE METHOD

IVY'S METHOD

Principle: under fixed pressure three standard punctures are produced on the volar aspect of the forearm by using microlancet and the average time taken for the bleeding to stop from the puncture sites is measured.

INSTRUMENTS USED:

1. Sphygmomanometer
2. Sterile disposable microlancet –having cutting depth of 2.5 mm and width of 1.0mm
3. Stop watch
4. Filterpaper

PROCEDURE:

- A Sphygmomanometer cuff is put around the patient's upper arm and pressure is fixed to 40 mm Hg by inflating the cuff.
- With antiseptic 70% ethanol ,the dorsal surface of the forearm is cleaned
- Three punctures are done by using microlancet at 5-10 cm apart.
- One stopwatch is used for each puncture.As soon as the puncture is made the stopwatch is started.
- By using the filter paper bloodoozingfrom the wound is blotted. Direct touching of the edges of the wound should be avoided.
- The timer is stopped when there is no stains in the filter paper.
- Time taken for bleeding to stop from all three puncture wound is noted. The average time is recorded as the bleeding time
- Sterile adhesive strip is placed over the sites of puncture.
- Normal bleeding time :2-7 minutes.

Conditions producing prolonged bleeding time are

- Low platelet count
- Platelet function disorders
- Von Willebrand disease
- Disorders of blood vessels.

DUKE'S METHOD

It is done by puncturing of ear lobe. Since it produces large haematoma it is not in use.

TEMPLATE METHOD

In this method larger cut is made with the help of surgical blade and the wound is 5mm long and 1mm deep. It produces a large scar.

PLATELET COUNT

Platelet count can be done by manual method or by using of automated haematology analyser.

MANUAL COUNT:

Blood is collected from the vene puncture and the anticoagulant used is dipotassium salt of ethylene diaminetetraacetic acid (EDTA). EDTA is a choice of anticoagulant because it chelates the calcium ions and minimize platelet adherence and clumping.

By doing platelet count estimation the factors to be considered are

1. They should be separated from the dust particles or fragments of red blood cells.
2. They are very small in size.
3. They will have a tendency to aggregate together or adhere to the glass ware.
4. Capillary blood should be avoided since platelets adhere at the site of wound and gives false low platelet count.

METHODS:

- Anticoagulated venous blood is thoroughly mixed with diluent in the ratio of 20:1.
- Charge the improved Neubauer counting chamber.
- Place the mounted counting chamber inside a moist chamber and leave it undisturbed for 20 minutes. This is for settling of platelets and for the prevention of drying of fluid.
- Platelet is counted by using microscope with 40x objectives in the central large square. Platelets are round or oval, small bluish brightly refractile fragments.

Problems encountered in the peripheral smear examination of platelets are platelet clumps, platelet satellitism on white blood cells and poor smearing.

AUTOMATED METHOD:

Principle used by this method is principle of aperture impedance. This method was first introduced by Coulter Electronics and so it is called as coulter principle.

TESTS TO ASSESS THE COAGULATION SYSTEM

1. Clotting Time
2. Prothrombin Time
3. Activated partial thromboplastin Time

CLOTTING TIME:

Methods:

Wright's capillary tube method

- Under sterile precautions a deep prick is made in the finger tip. Time is noted when bleeding starts by starting the stop watch.
- The blood drop at the fingertip is touched with one end of the capillary tube which is kept tilted downwards.
- The tube is filled by capillary action.
- After about two minutes small lengths of the tube are snapped off at intervals of 15 seconds and each time it is noted whether the fibrin thread is formed between the ends of snapped tube.
- When the fibrin thread is first seen time is noted

Lee and White method

- Two unsiliconised glass tubes with 10mm external bore should be prewarmed by keeping at 37° C bath.
- Blood is drawn from anticubital vein by a clean venepuncture. As soon as blood enters the syringe two stop watches are started. 2-2.5 mL of blood is collected and 1mL of blood is poured into each tube after removing the needle.

- Tubes are kept at 37°C for 2 minutes and are gently inclined at 1 minute interval until one can be tilted at an angle >90°C without spilling or flowing out of blood.
- The stopwatch is stopped. Similarly, this is done with second tube simultaneously.
- Clotting time is expressed as mean of the two readings.

Normal Clotting Time is 4-9 minutes.

PROTHROMBIN TIME (PT) AND INTERNATIONAL NORMALISED RATIO (INR):

Measures the time taken for fibrin formation through extrinsic and common pathways of coagulation. It measures the activity of factor VII, factor V, factor X, factor II and fibrinogen.

Principle:

Prothrombin Time is usually done with Activated Partial Thromboplastin Time. Prothrombin Time is discovered by Dr. Armand Quick and colleagues in 1935. Dr. Paul Owren named as “p and p” or prothrombin and proconvertin method.

Collection of blood for the PT test by using siliconized glass or polypropylene syringe with large bore needle (20Gauge or 21Gauge). Venous blood is collected from the syringe, needle is removed and the blood is passed gently in the anticoagulant containing tube. For collection

of blood, glass syringes should be avoided and also blood should not be drawn from the indwelling catheter.

Anticoagulant used is 3.8% sodium citrate solution. Blood to anticoagulant solution ratio is 9:1. Purpose of using sodium citrate is that it binds with calcium.

Reagent used for testing the prothrombin time is Thromborel S. It is prepared from human placenta. Composition of this reagent is lyophilized human placental thromboplastin (≤60g/L), calcium chloride (approximately 1.5g/L). Unopened reagent should be stored at 2 to 8^0 C.

Blood is centrifuged to separate the plasma for 15-20 minutes at 3000 revolutions per minute. Plasma is analysed by an automated instrument and the prothrombin time is measured. Plasma should be tested within 24 hours of collection.

INR:

It was invented in early 1980's by Tom Kirkwood at UK National Institute for Biological Standards and Control. It is used to standardize prothrombin time.

$$\text{INR} = \left(\frac{\text{Patient PT}}{\text{Mean PT}} \right)^{\text{ISI}}$$

Patient PT is measured and the mean PT is obtained by calculating the geometric mean PT of 20 healthy persons including both male and female tested at same laboratory.

ISI (International Sensitivity Index) of a particular tissue thromboplastin is derived by comparing it with a reference thromboplastin of known ISI. It is a sensitivity index specific to each reagent instrument combination.

The reference range for PT is 12-13 seconds. For INR the reference range is 0.8-1.2 seconds.

ACTIVATED PATIAL THROMBOPLASTIN TIME:

The older name is kaolin Cephalin Time. It was first described in 1953 by researchers at The University of North Carolina at Chapel Hill. This test measures the clotting time of plasma after activation of contact factors and addition of phospholipid and calcium chloride. Phospholipid used for activation of the plasma and the calcium is used to reverse the effect of sodium citrate which is the anticoagulant used. This test measures the efficacy of intrinsic and common pathway of coagulation. Normal APTT time requires the following coagulation factors, factor I, II, V, VIII, IX, X, XI and XII.

Reagents Used for Testing APTT:

Activated Cephaloplastin reagent:

It is extracted from dehydrated rabbit brain in ellagic acid. Store the closed container at +2 to +8 °C. It activates the factors of intrinsic coagulation system in measuring APTT.

Calcium Chloride:

It is a ready to use solution standardized at 0.025 mol/l concentration. On activation of contact factors by the activator in the APTT reagents, Factor XIIa is produced that cleaves factor XI to XIa. The partial thromboplastin time is then measured by adding appropriate amount of Calcium Chloride.

Samples are collected and plasma is prepared as for that of prothrombin time test. By automated analyser APTT is measured. The normal range is 28-32 seconds.

DESIGN, METHODOLOGY AND TECHNIQUES

1. SOURCE OFDATA:

Pregnant women with pregnancy induced hypertension admitted in The Department of Obstetrics, Coimbatore Medical College Hospital, Coimbatore.Normal pregnant women, attending outpatient clinic in the Department of Obstetrics, Coimbatore Medical College Hospital, Coimbatore.

2.STUDY PLACE:

The Department of Pathology, Coimbatore Medical College Hospital, Coimbatore.

3.STUDY PERIOD:

Prospective study from July 2013 toJuly2014.

4. STUDY DESIGN:

Case control study

5. SAMPLE SIZE:

120

6. INCLUSION CRITERIA:

Normotensive pregnant women consist of 60 persons.

Pregnancy induced hypertension patients are divided into two groups.

GROUP I: Non severe pregnancy induced hypertension-30 cases.

GROUP II: Severe pregnancy induced hypertension-30 cases.

7. EXCLUSION CRITERIA:

- Previous history of hypertension.
- Previous history of diabetes mellitus.
- Previous history of renal disease.
- Previous history of coagulation abnormalities

METHODOLOGY:

Study conducted at Coimbatore Medical College, Coimbatore from July 2013 to July2014. Study group consists of 120 pregnant women from the department of obstetrics, Coimbatore Medical College. In which 60 pregnant women were selected for control group with normal blood pressure .The remaining 60 pregnant women with systolic blood pressure of 140 mmHg and above and diastolic blood pressure of 90mmHg and above. Both the groups were in the same age group that is between 20 to 30 years and the period of pregnancy which is between 36 to 39 weeks. Both study groups were matched.

Those with blood pressure 140/90mmHg and above are divided in to two groups.The nonsevere PIH group consists of 30pregnant women with blood pressure between 140/90mmHg and 160/110mmHg. The severe PIH group consists of 30 pregnant women with systolic blood pressure above 160mmHg and diastolic blood pressure above 110mmHg with symptoms like vomiting, headache,Visual Disturbances, Upper

abdominal Pain, Oliguria, Convulsion, Low platelet Count, Elevated serum enzymes and creatinine.

Detailed medical and obstetric history taken from the study group and procedure explained. After getting consent, the following tests were done.

1. Bleeding time –By DUKE'S method.
2. Clotting time –Wright' capillary tube method.
3. Platelet count-By Automated Haematology Analyser SYSMEX XP-100.
4. Prothrombin Time and APTT- By using Automated Analyser SYSMEX CA-50.

Platelet Count Estimation Method:

1. Collect venous blood sample with EDTA anticoagulant.
2. Make sure that Ready is displayed on the instrument status indicator at the top of the display area and analysis mode is set to whole blood mode.
3. Mix the sample by inverting the sample tube.
4. Remove the cap while taking care not allow blood scatter.
5. Set the tube to the sample probe, and in that condition, press the start switch.

6. The analysis starts, the status display indicates Aspirating. When sample aspiration is completed, status display changes to Running. When Running is displayed the sample can be removed safely.
7. The analysis results are displayed 60 seconds after starting the analysis.

Figure: Vaccutinor used for the collection of blood for the estimation of platelet count.

Vaccutinor contains anticoagulant EDTA.Blood is collected and platelet count estimation done by autoanalyzer.

Figure: Analyser used for estimation of platelet count

By this analyser platelet count is estimated by automated method.

PROTHROMBIN TIME:

1. 2ml Venous blood is collected with anticoagulant trisodium citrate and centrifuged to get plasma. By using automated blood coagulation analyser sysmex CA 50 prothrombin time is measured from the plasma by the following steps.
2. Add 50 µl of blood sample into the cuvette and press start button.
3. Wait for beep after one minute and then add 100 µl of prothrombin time reagent and close the lid. Note the reading from the analyser.

ACTIVATED PARTIAL THROMBOPLASTIN TIME

2ml Venous blood is collected with anticoagulant trisodium citrate and centrifuged to get plasma. By using automated blood coagulation analyser sysmex CA 50 activated partial thromboplastin time is calculated from the plasma by the following steps.

1. Add 50 µl of blood sample into the cuvette and press start button.
2. Wait for the beep after one minute add 50 µl of activated partial thromboplastin time reagent and close the lid.
3. Wait for the beep after 3 minutes and then add 50 µl of calcium chloride forcibly into the cuvette and close the lid.
4. Note the reading from the analyser.

Figure: Vaccutinor used for collection of blood for PT and APTT.

It contains 3.8% sodium citrate solution as an anticoagulant. Used for estimation of prothrombin time and activated partial thromboplastin time.

Figure: Reagents used for estimation of prothrombin time and activated partial thromboplastin time.

Calcium chloride and Actin are used for estimation of activated partial thromboplastin time.

Thromborel S is used for estimation of prothrombin time.

Figure: Analyser used for estimation of prothromin time and activated partial thromboplastin time.

By this analyser PT, APTT and fibrinogen levels are estimated by automated method.

OBSERVATION AND RESULTS

Statistical methods used for analysis of Coagulation Parameters include SPSS 18 software, Anova, Scheffe, Post Hoc test and one way

Bleeding time (in seconds):

Table 1: Distribution of patients according to Bleeding Time:

BLEEDING TIME (seconds)	CLINICAL DIAGNOSIS						TOTAL
	Normal pregnancy	%	PIH Non severe	%	PIH severe	%	
110-150	30	50	02	7	00	0	32
150-190	27	45	20	67	00	0	47
190-230	03	5	08	27	15	50	26
230-260	00	0	00	0	15	50	15
Total	**60**	**100**	**30**	**100**	**30**	**100**	**120**

Normal Pregnancy- among 60 normal pregnant women, 30 women (50%) showed BT between 110-150 seconds.27 women (45%) revealed BT between 150-190 seconds and 3(5%) revealed BT between 190-230 seconds.

Nonsevere PIH- among 30 cases, 2 (7%) cases revealed BT between 110-150 seconds, 20(67%) cases showed BT between 150-190 seconds and 8(27%) cases showed BT between 190-230 seconds.

Severe PIH-Among 30 cases, 15(50%) cases revealed BT between 110-150 seconds, 15(50%) cases showed BT between 150-190 seconds.

Table 2: Mean Bleeding Time for Normal Pregnancy, Non Severe PIH and Severe PIH Patients.

Bleeding time (in seconds)

	Number	**Mean**	**Std.Deviation**	**Std.Error**
Normal Pregnancy	60	153.5333	23.95014	3.09195
Non Severe PIH	30	178.5333	23.83815	4.35223
Severe PIH	30	227.4667	21.21114	3.87261
Total	**120**	**178.2667**	**38.09491**	**3.47757**

Chart 1: The mean Bleeding Time of Normal Pregnancy, Non severe PIH and severe PIH.

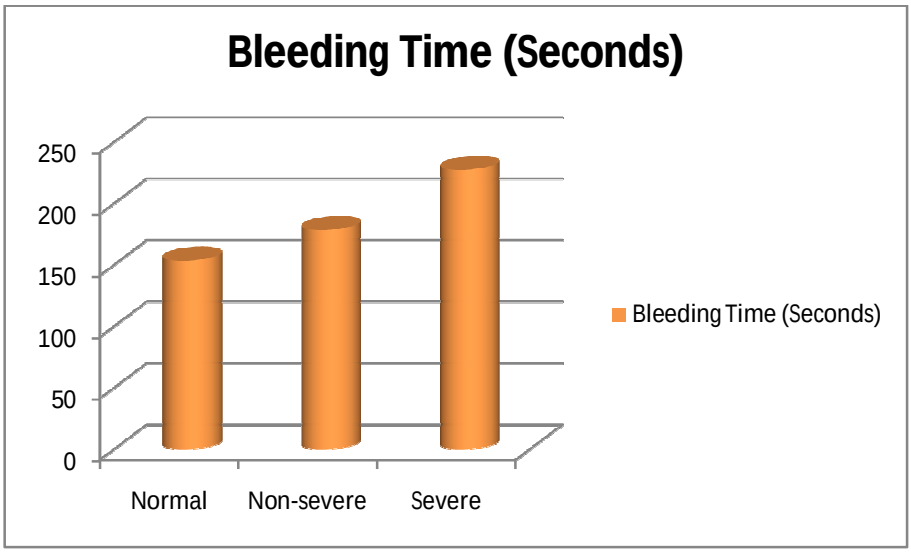


Table 3: Analysis of variance of Bleeding Time among group Normal Pregnancy, Non severe PIH and Severe PIH

Anova

	Sum of squares	**Df**	**Mean square**	**F**	**Sig**
Between Groups	109325.6	2	54662.800	100.924	0.000
Within Groups	63369.867	117	541.623		
Total	**172695.5**	**119**			

Table 4: Multiple Comparisons of Bleeding time among group Normal Pregnancy, Non severe PIH and Severe PIH

Dependant variable: Bleeding Time (Seconds)

Scheffe

(I)Blood Pressure	(J)Blood Pressure	Mean Difference (I-J)	Std. Error	Sig.
Normal Pregnancy	Non Severe PIH	-25.00000*	5.20395	0.000
	Severe PIH	-73.93333*	5.20395	0.000
Non Severe PIH	Normal Pregnancy	25.00000*	5.20395	0.000
	Severe PIH	-48.93333*	6.00901	0.000
Severe PIH	Normal Pregnancy	73.93333*	5.20395	0.000
	Non Severe PIH	48.93333*	6.00901	0.000

*. The mean difference is significant at the 0.05 level.

From the above tables the mean bleeding time of normal pregnancy, for the non-severe PIH and for the severe PIH were 153.53 seconds, 178.53 seconds and 227.46 seconds respectively.

The F value 100.924 for the mean difference in the Bleeding time between the normal pregnancy, nonsevere PIH and severe PIH patients were significant.(p value <0.001). Further post hoc analysis revealthat the patients with severe PIH showed prolonged bleeding time compared to non-severe PIH and normotensive pregnant women.

CLOTTING TIME

Table 5: Distribution of patients according to Clotting Time

CLOTTING TIME (seconds)	CLINICAL DIAGNOSIS						TOTAL
	Normal pregnancy	%	PIH Non severe	%	PIH severe	%	
210-260	20	33	12	40	12	40	44
260-310	14	23	08	27	10	33	32
310-360	12	20	06	20	03	10	21
360-410	08	14	04	13	03	10	15
410-460	03	5	00	0	02	7	05
460-510	03	5	00	0	00	0	03
Total	**60**	**100**	**30**	**100**	**30**	**100**	**120**

The above table showed the normal pregnancy constitutes 60 women,in which 20 had CT between 210-260seconds,14 had CT between

260-310 seconds, 12 showed CT between 310-360 seconds,8 revealed CT between 360-410 seconds,3 showed CT between 410- 460 and 3 had CT between 460-510.

Non severe PIH-The above table showed 30 cases in which 12 had CT between 210-260seconds,8 had CT between 260-310 seconds, 6 showed CT between 310-360 seconds and4 revealed CT between 360-410 seconds.

Severe PIH-The above table showed 30 cases in which 12 had CT between 210-260seconds,10 had CT between 260-310 seconds, 3 showed CT between 310-360 seconds,3 revealed CT between 360-410 seconds and 2had CT between 410-460 seconds.

Table 6: Mean Clottingtime (in seconds) for Normal Pregnancy, Non Severe PIH and Severe PIH Patients.

	Number	**Mean**	**Std.Deviation**	**Std.Error**
Normal Pregnancy	60	310.5667	70.73857	9.13231
Non Severe PIH	30	290.2000	55.07950	10.05610
Severe PIH	30	292.4000	61.90850	11.30289
Total	**120**	**300.9333**	**65.18026**	**5.95012**

Chart 2: The mean Clotting Time of Normal Pregnancy, Non severe PIH and severe PIH.

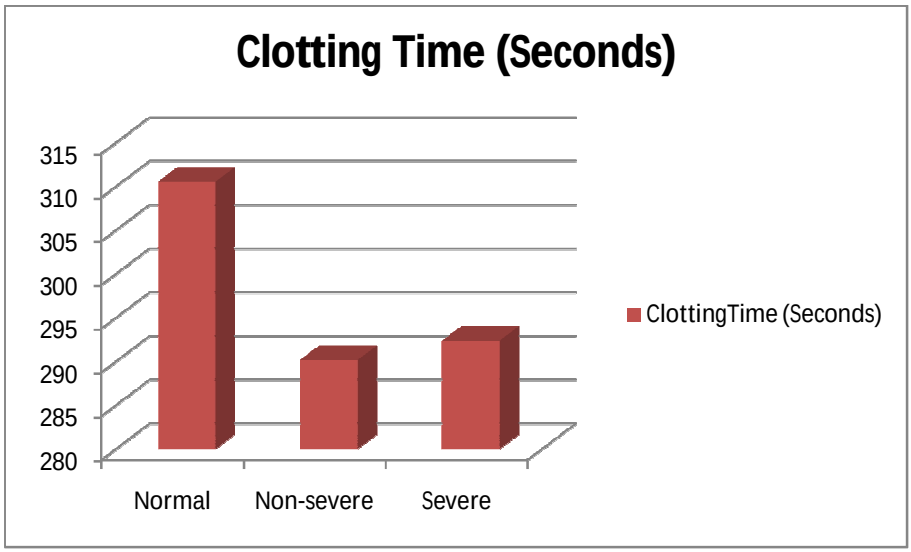


Table 7: Analysis of variance of Clotting Time among group Normal Pregnancy, Non severe PIH and Severe PIH

Anova

	Sum of squares	**Df**	**Mean square**	**F**	**Sig**
Between Groups	11208.733	2	5604.367	1.326	0.269
Within Groups	494358.7	117	4225.288		
Total	**505567.5**				

Table 8: Multiple Comparisons of Clotting time among group Normal Pregnancy, Non severe PIH and Severe PIH

Dependant variable: ClottingTime (Seconds)

Scheffe

(I)Blood Pressure	(J)Blood Pressure	Mean Difference (I-J)	Std. Error	Sig.
Normal Pregnancy	Non Severe PIH	20.36667	14.53494	0.378
	Severe PIH	18.16667	14.53494	0.460
Non Severe PIH	Normal Pregnancy	-20.36667	14.53494	0.378
	Severe PIH	-2.20000	16.78350	0.991
Severe PIH	Normal Pregnancy	-18.16667	14.53494	0.460
	Non Severe PIH	2.20000	16.78350	0.991

From the above tables the mean clotting time of nomal pregnancy, nonsevere PIH and severe PIH patients were 310.56 seconds,290 seconds and 292 seconds respectively.

In the above tables the F value for the mean difference in the clotting time between the normal pregnancy,nonsevere PIH and severe PIH were not significant.(P value 0.269)

PLATELET COUNT:

Table 9: Distribution of patients according to Platelet Count

PLATELET COUNT (lacs/mm^3)	CLINICAL DIAGNOSIS						TOTAL
	Norma pregnancy	%	PIH Non severe	%	PIH severe	%	
0.6-1.6	02	3	02	7	18	60	22
1.6-2.6	14	23	24	80	12	40	50
2.6-3.6	34	57	04	13	00	0	38
3.6-4.3	10	17	00	0	00	0	10
Total	**60**	**100**	**30**	**100**	**30**	**100**	**120**

Table10 : Mean Platelet Count (Lakhs) for Normal Pregnancy, Non Severe PIH and Severe PIH Patients.

	Number	**Mean**	**Std. Deviation**	**Std.Error**
Normal Pregnancy	60	2.8950	0.76469	0.10259
Non Severe PIH	30	2.1707	0.55797	0.10187
Severe PIH	30	1.5880	0.57666	0.10528
Total	**120**	**2.3872**	**0.87914**	**0.08025**

Chart 3: The mean Platelet Count of Normal Pregnancy, Non severe PIH and severe PIH.

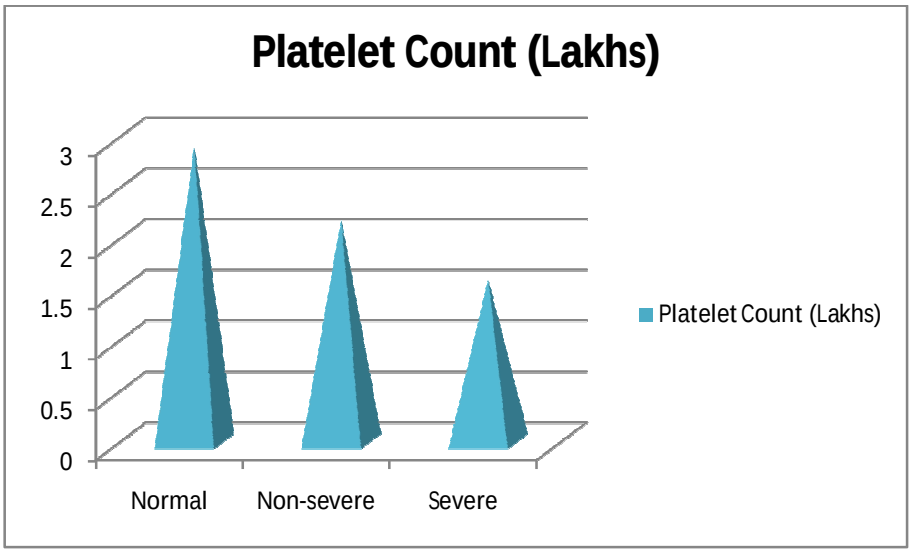


Table 11: Analysis of variance of Platelet Count among group Normal Pregnancy, Non severe PIH and Severe PIH

Anova

	Sum of squares	**Df**	**Mean square**	**F**	**Sig**
Between Groups	36.040	2	18.020	37.694	0.000
Within Groups	55.933	117	0.478		
Total	**91.973**	**119**			

Table 12: Multiple Comparisons of Platelet Count among group Normal Pregnancy, Non severe PIH and Severe PIH

Dependant variable: Platelet Count (Lakhs)

Scheffe

(I)Blood Pressure	(J)Blood Pressure	Mean Difference(I-J)	Std. Error	Sig.
Normal Pregnancy	Non Severe PIH	0.72433*	0.15461	0.000
	Severe PIH	1.30700*	0.15461	0.000
Non Severe PIH	Normal Pregnancy	-0.72433*	0.15461	0.000
	Severe PIH	0.58267*	0.17852	0.006
Severe PIH	Normal Pregnancy	-1.30700*	0.15461	0.000
	Non Severe PIH	-0.58267*	0.17852	0.006

*. The mean difference is significant at the 0.05 level

From the above table the mean platelet count of normal pregnancy, nonsevere PIH and severe PIH patients were 2.89 lacs/cumm,2.17lacs/cumm and 1.58 lacs/cumm were respectively.

The F value for the mean difference in the platelet count between the normal pregnancy,nonsevere PIH and severe PIH patients were significant.(P value <.000).

Further the Post Hoc Test analysis reveals that the patients with severe PIH show decrease in platelet count compared to nonsevere PIH and normal pregnancy groups.

PROTHROMBIN TIME:

Table 13: Distribution of patients according to Prothrombin Time:

PROTHROMBIN TIME (seconds)	CLINICAL DIAGNOSIS						TOTAL
	Normal pregnancy	%	PIH Non severe	%	PIH severe	%	
8-10	10	17	15	50	03	10	28
10-12	36	60	12	40	06	20	54
12-14	14	23	03	10	15	50	32
14-20	00	0	00	0	06	20	06
Total	**60**	**100**	**30**	**100**	**30**	**100**	**120**

Table14 : Mean Prothrombin time (in seconds) for Normal Pregnancy, Non Severe PIH and Severe PIH Patients.

	Number	**Mean**	**Std.Deviation**	**Std.Error**
Normal Pregnancy	60	11.1050	1.36797	0.17660
Non Severe PIH	30	10.1933	1.53801	0.28080
Severe PIH	30	13.0667	2.74846	0.50180
Total	**120**	**11.3675**	**2.11076**	**0.19269**

Chart 4: The mean Prothrombin Time of Normal Pregnancy, Non severe PIH and severe PIH.

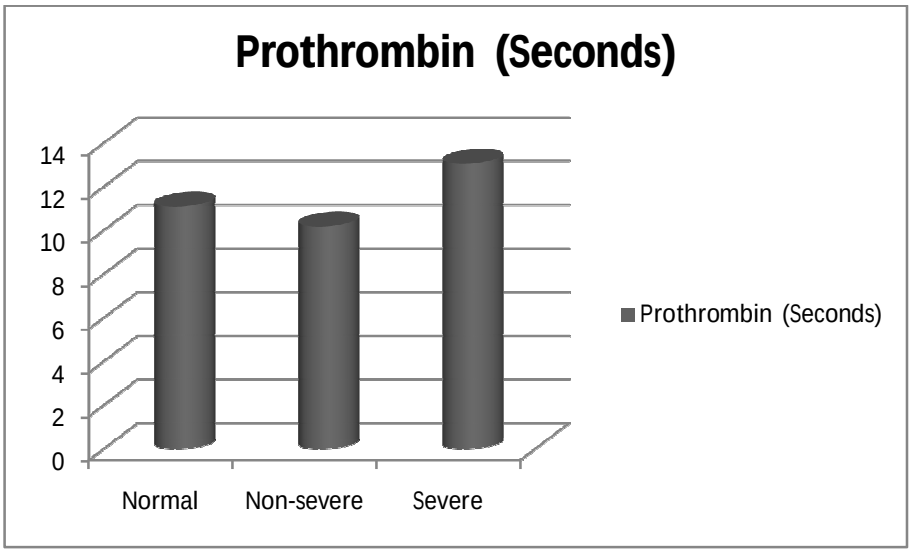


Table 15: Analysis of variance of Prothrombin Time among group Normal Pregnancy, Non severe PIH and Severe PIH

Anova

	Sum of squares	**Df**	**Mean square**	**F**	**Sig**
Between Groups	132.109	2	66.055	19.414	0.000
Within Groups	398.074	117	3.402		
Total	**530.183**	**119**			

Table 16: Multiple Comparisons of Prothrombin Time among group Normal Pregnancy, Non severe PIH and Severe PIH

Dependant variable: ProthrombinTime (Seconds)

Scheffe

(I)Blood Pressure	(J)Blood Pressure	Mean Difference (I-J)	Std. Error	Sig.
Normal Pregnancy	Non Severe PIH	0.91167	0.41245	0.091
	Severe PIH	-1.96167*	0.41245	0.000
Non Severe PIH	Normal Pregnancy	-0.91167	0.41245	0.091
	Severe PIH	-2.87333*	0.47626	0.000
Severe PIH	Normal Pregnancy	1.96167	0.41245	0.000
	Non Severe PIH	2.87333*	0.47626	0.000

*. The mean difference is significant at the 0.05 level

From the above table the mean prothrombin time of normal pregnancy,nonsevere PIH and severe PIH were 11.0 seconds, 10.19 seconds and 13.066 respectively.

The F value for the mean difference in the prothrombin time between the normal pregnancy,nonsevere PIH and severe PIH patients were significant.(P value <0.000).

Further Post Hoc Test analysis show that patients with severePIH show increase in prothrombin time.

Activated Partial Thromboplatin Time:

Table 17: Distribution of patients according to APTT:

APTT (seconds)	CLINICAL DIAGNOSIS						TOTAL
	Normal pregnancy	%	PIH Non severe	%	PIH severe	%	
22-25	11	18	04	13	03	10	18
25-28	10	17	06	20	05	17	21
28-31	21	35	08	27	06	20	35
31-36	18	30	12	40	10	33	40
36-40	00	0	00	0	06	20	06
Total	**60**	**100**	**30**	**100**	**30**	**100**	**120**

Table 18 : Mean APTT (in seconds) for Normal Pregnancy, Non Severe PIH and Severe PIH Patients.

	Number	**Mean**	**Std.Deviation**	**Std.Error**
Normal Pregnancy	60	29.3633	3.78999	0.48929
Non Severe PIH	30	29.5000	3.78080	0.69028
Severe PIH	30	32.2867	5.44836	0.99473
Total	**120**	**30.1283**	**4.40548**	**0.40216**

Chart 5: The mean APTT of Normal Pregnancy, Non severe PIH and severe PIH.

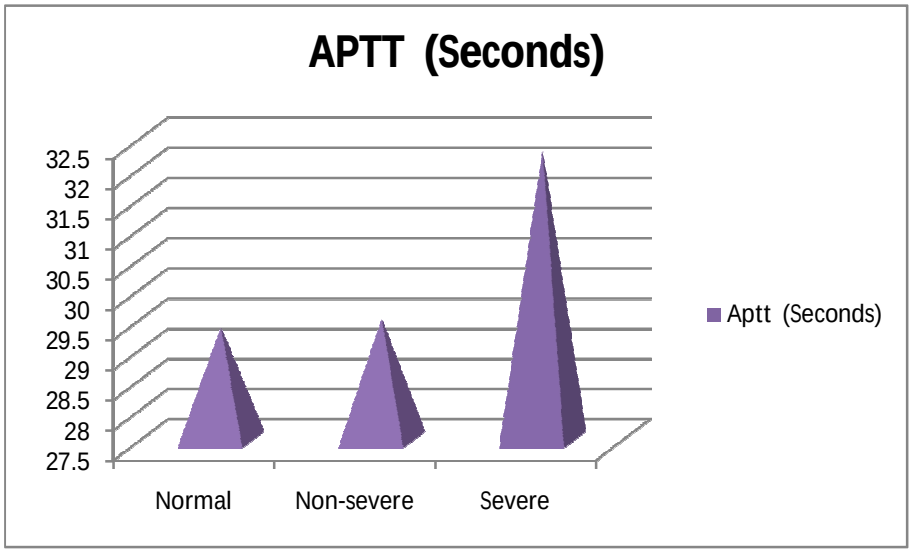


Table 19: Analysis of variance of APTT among group Normal Pregnancy, Non severe PIH and Severe PIH

Anova

	Sum of squares	**Df**	**Mean square**	**F**	**Sig**
Between Groups	186.710	2	93.355	5.145	0.007
Within Groups	2122.874	117	18.144		
Total	**2309.584**	**119**			

Table 20: Multiple Comparisons of APTT among group Normal Pregnancy, Non severe PIH and Severe PIH

Dependant variable: APTT (Seconds)

Scheffe

(I)Blood Pressure	(J)Blood Pressure	Mean Difference (I-J)	Std. Error	Sig.
Normal Pregnancy	Non Severe PIH	-0.13667	0.95248	0.990
	Severe PIH	-2.92333*	0.95248	0.011
Non Severe PIH	Normal Pregnancy	0.13667	0.95248	0.990
	Severe PIH	-2.78667*	1.09982	0.044
Severe PIH	Normal Pregnancy	2.92333*	0.95248	0.011
	Non Severe PIH	2.78667*	1.09982	0.044

*. The mean difference is significant at the 0.05 level

From the above table the mean APTT of normal pregnancy,nonsevere PIH and severe PIH patients were 29.36 seconds,29.5seconds and 32.28 seconds were respectively.

The F value for the mean difference between normal pregnancy, nonsevere PIH and severe PIH patients were significant. (P value 0.007).

Further Post Hoc Test analysis reveals patients with severe PIH show increased in APTT value compared to normal pregnancy and nonsevere PIH

DISCUSSION

Bleeding Time:

Present study showed the mean bleeding time for normal pregnancy, non-severe PIH and severe PIH were 153 seconds, 178 seconds and 227 seconds respectively. P-value <0.000 is significant.

Priyanka Chauchan[100] et al 2014 study showed bleeding time for normal pregnancy, nonsevere PIH and severe PIH were 180 seconds, 294 seconds and 324 seconds respectively, with significant p-value (<0.001). So this study correlated well with present study.

Clotting Time:

Present study showed the mean clotting time for normal pregnancy was 310 seconds, clotting time for the non-severe PIH was 290 seconds and the severe PIH was 292 seconds, the P-value 0.269 is not significant.

The mean clotting time compared with Priyanka Chauchan et al 2014 study, which showed the mean clotting time for normal pregnancy was 358 seconds, for the non-severe PIH was 368 seconds and for the severe PIH was 378 seconds. P-value more than 0.05 was not significant.

There will be interobserver variations in doing clotting time estimation.

Platelet Count:

In the present study the mean platelet count of normal pregnancy, non-severe PIH and severe PIH patients were 2.89 lakhs/cubic mm, 2.17 lakhs/cubic mm and 1.58 lakhs/cubic mm respectively, with significant P-value 0.000. These values correlated with following studies:

Shete Anjali [101] et al 2013 study showed the mean platelet count in normal pregnancy was 3.41 lakhs/cubic mm and in severe PIH 1.27 lakhs/cubic mm and the significant P-value <0.05.

Bhia Namavar Jahrom[47] et al 2009 revealed the mean platelet count of normal pregnancy and severe PIH were 2.33 lakhs/cubis mm and 1.5 lakhs/ cubic mm with significant P-value <0.001.

Sameer[102] et al April 2014 indicated the mean platelet count in normal pregnancy was 2.39 lakhs/cubic mm and severe PIH was 1.6 lakhs/cubic mm with significant P-value <0.001.

Priyanka Chauchan[100] et al 2013 study exhibited the mean ± standard deviation of platelet count in normal pregnancy was 2.47 ± 0.75 lakhs/cubic mm, mean ± standard deviation of platelet count in nonsevere PIH was 1.62 ± 0.678 lakhs/cubic mm and mean ± standard deviation of platelet count in severe PIH 1.63 ± 0.742 lakhs/cubic mm. The P-value was significant (<0.001).

Elloradevi[103] et al 2012 revealed the platelet count in normal pregnancy, nonsevere PIH and severe PIH were 2.44 ± 0.11 lakhs/cubic

mm, 1.82 ± 0.19 lakhs/ cubic mm and 1.42 ± 0.23 lakhs/ cubic mm respectively with significant P-value <0.05.

S. Mohapatra[104] et al exhibited the mean platelet count in normal pregnancy was 2.38 ± 0.33 lakhs/cubic mm , mean platelet count in nonsevere PIH was 1.82 ± 0.45 lakhs/cubic mm and mean platelet count in severe PIH 1.21 ± 0.49 lakhs/cubic mm with P-value of <0.1.

Studies above mentioned were correlated well with present study for the mean platelet count and the P-value.

Prothrombin time:

In present study the mean prothrombin time for normal pregnancy, non-severe PIH and severe PIH patients were 11.05 seconds, 10.19 seconds and 13.06 seconds respectively, with significant P-value <0.000.

Wale Mohamed Aref[105] et al 2012 study showed the mean prothrombin time for normal pregnancy and severe PIH patients were 13.24 ± 0.86 seconds and 13.41 ± 0.68 seconds respectively, with P-value more than 0.05

Tashin Mushtaque [106] et al 2013 study revealed the mean prothrombin time for normal pregnancy, Non severe PIH and severe PIH patients were 10.9 seconds, 10.1 seconds and 9.8 seconds respectively, with P-value less than 0.0001 was statistically significant

The above two studies statistically correlated with present study.

APTT:

In present study the mean APTT for normal pregnancy, non-severe PIH and severe PIH patients were 29.3 seconds, 29.5 seconds and 32.2 seconds respectively, with significant P-value <0.007.

Tashin Mushtaque [106] et al 2013 study revealed the mean APTT for normal pregnancy, Non severe PIH and severe PIH patients were 26.68 seconds, seconds 26.71 and 26.25 seconds respectively, with P-value less than 0.005 was statistically significant.

The present study correlated well with the above study.

SUMMARY

Study conducted at Coimbatore Medical College, Coimbatore during the year 2013-2014. The thesis study titled as “COAGULATION PROFILE STUDY IN PREGNANCY INDUCED HYPERTENSION”. It is a case control prospective study in which 60 control groups and 60 study groups. Control group includes normotensive pregnant woman and study group consists of two groups, one is Non Severe PIH and the other is Severe PIH. For all the groups coagulation parameters which includes BT, CT, Platelet Count, PT and APTT were done. Statistical analysis done which were compared with various available previous studies.

- Present study showed the mean bleeding time for normal pregnancy, nonsevere PIH and severe PIH were 153 seconds, 178 seconds and 227 seconds respectively. P-value less than 0.000 is significant.
- Present study showed the mean clotting time for normal pregnancy was 310 seconds, clotting time for the nonsevere PIH was 290 seconds and the severe PIH was 292 seconds, the P-value 0.269 is not significant.
- In the present study the mean platelet count of normal pregnancy, nonsevere PIH and severe PIH patients were 2.89 lakhs/cubic mm,

2.17 lakhs/cubic mm and 1.58 lakhs/cubic mm respectively, with significant P-value less than 0.000.

- In present study the mean prothrombin time for normal pregnancy, non-severe PIH and severe PIH patients were 11.05 seconds, 10.19 seconds and 13.06 seconds respectively, with significant P-value less than 0.000.
- In present study the mean APTT for normal pregnancy, nonsevere PIH and severe PIH patients were 29.3 seconds, 29.5 seconds and 32.2 seconds respectively, with significant P-value less than 0.007.

CONCLUSION

- Present study revealed changes in the coagulation parameters in women with severe pregnancy induced hypertension which was compared to normotensive pregnant women and in women with non-severe pregnancy induced hypertension.
- Platelet count showed inverse relationship with severity of pregnancy induced hypertension.
- Bleeding time, Prothrombin time and Activated Partial Thromboplastin time showed prolonged values with severe pregnancy induced hypertension.
- With increasing severity of blood pressure in pregnant women changes noted in the coagulation parameters.
- Current maternal mortality in India is 212 per one lakh live births and in Tamil Nadu it is 178 per one lakh live births.
- Coagulation abnormalities include HELLP syndrome and disseminated intra vascular coagulation contribute the causes for maternal deaths in pregnancy induced hypertension.
- Present study can be helpful in identifying the coagulation abnormalities in relation to pregnancy induced hypertension in

earlier stage and can be helpful for the management of complications in relation to pregnancy induced hypertension.

- Maternal and fetal mortality and morbidity can be reduced with the help of this study.

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ANNEXURE-1

DEPARTMENT OF PATHOLOGY,

COIMBATOREMEDICAL COLLEGE

HOSPITAL,COIMBATORE

PROFORMA

COAGULATION PROFILE STUDY IN PREGNANCY INDUCED HYPERTENSION

NAME : OP/ID NO :

AGE : DEPARTMENT :

SEX :

OCCUPATION :

ADDRESS :

1) Clinical Details

a) Complaints/ period of amenorrhoea

b) Past History

c) Past Obstetrics History

d) Menstrual History

e) Family History

f) General Examination BP

g) Systematic Examination

CVS

RS

CNS

PA

2) Investigations

a) Routine HB, Urine

b) USG Examination

3) Clinical Diagnosis

4) Coagulation

Parameter Analysis

Bleeding Time

Clotting Time

Platelet Count

Prothrombin Time and

Activated Partial Thromboplastin Time

KEY TO MASTER CHART

APTT	-	Activated Partial Thromboplastin Time
P	-	Primi
G2P1	-	Gravida 2 Para 1
NP	-	Normal Pregnancy
NSPIH	-	Non Severe Pregnancy Induced Hypertension
SPIH	-	Severe Pregnancy Induced Hypertension

ANNEXURE-III

CONSENT FORM

Dr.S.VIJAYALAKSHMI, postgraduate student in the Department of Pathology, Coimbatore Medical College Hospital is conducting a study on **"COAGULATION PROFILE STUDY IN PREGNANCY INDUCED HYPERTENSION".**The study and test procedures were explained to me clearly. I hereby give my consent to participate in this study and to give blood sample. The data obtained herein may be used for research and publication.

Name:

Place:

Signature:

ஒப்புதல் படிவம்

எனக்கு இரத்தம் எடுத்து பரிசோதனை செய்ய
முழு மனதுடன் சம்மதிக்கிறேன்

இப்படிக்கு

நாள் :
இடம் :

MASTER CHART

Sl.No	NAME	AGE	IP.No	OBSTETRICS SCORE	GESTATIONAL AGE	HEADACHE	EDEMA	VISUAL DISTURBANCES	VOMITING	EPIGASTRIC PAIN	CONVULSIONS	BLOOD PRESSURE	URINE ALBUMIN	CLINICAL DIAGNOSIS	BLEEDING TIME	PLATELET COUNT	CLOTTING TIME	PROTHROMBIN TIME	APTT
1	Anu	23	47537	P	37	-	-	-	-	-	-	110/70	-	NP	156	1.58	278	8.7	22.2
2	Manju	23	47573	P	38	-	-	-	-	-	-	142/96	-	NSPIH	194	1.64	212	8.2	22.2
3	Banu	26	42943	P	38	-	-	-	-	-	-	116/72	-	NP	148	4.2	336	12.2	23.2
4	Abi	25	46552	P	37	-	-	-	-	-	-	120/70	-	NP	170	1.68	366	12.4	24.2
5	Divya	23	42943	G2P1	39	-	-	-	-	-	-	118/76	-	NP	144	3.24	274	9.3	24.6
6	Amsa	24	46749	P	39	-	-	-	-	-	-	148/94	Trace	NSPIH	178	1.72	392	8.4	23.2
7	Priya	28	43071	P	39	-	-	-	-	-	-	116/74	-	NP	180	2.68	466	11.2	30.6
8	Revathi	26	46576	G2P1	38	-	-	-	-	-	-	120/80	-	NP	136	3.12	334	11.2	30.8
9	Tamil selvi	28	47318	P	37	-	-	-	-	-	-	150/92	1+	NSPIH	182	1.86	216	8.6	24.2
10	Radhika	25	47417	G2P1	37	-	-	-	-	-	-	116/78	-	NP	176	2.42	376	11.6	28.6
11	Sangeetha	23	47385	G2P1	37	-	-	-	-	-	-	110/80	-	NP	142	3.94	222	11.8	30.8
12	Manimegalai	26	47676	P	39	-	-	-	-	-	-	156/100	-	NSPIH	112	2.42	246	9.2	22.4
13	Charulatha	29	47663	P	38	-	-	-	-	-	-	118/74	-	NP	144	2.64	248	10.2	30.6
14	Sujitha	24	47727	P	37	-	-	-	-	-	-	110/80	-	NP	220	2.76	252	11.6	30.4
15	Chellamal	25	47642	P	39	-	-	-	-	-	-	148/98	1+	NSPIH	154	1.74	236	9.4	25.2
16	Christy	27	48615	G2P1	38	-	-	-	-	-	-	120/70	-	NP	148	2.86	256	11.8	30.2
17	Jancy	27	48557	G2P1	38	-	-	-	-	-	-	110/70	-	NP	136	4.22	246	8.5	29.2
18	Sumathy	26	47631	P	38	-	-	-	-	-	-	162/110	Trace	SPIH	258	1.46	268	10.2	30.2
19	Lakshmi	25	8968	G2P1	38	-	-	-	-	-	-	112/72	-	NP	136	3.62	226	9.8	28.2
20	Chithra	24	38523	P	37	-	-	-	-	-	-	150/92	-	NSPIH	198	0.62	226	9.6	26.4
21	Fathima	23	36753	P	39	-	-	-	-	-	-	180/112	Trace	SPIH	246	1.52	272	9.2	30.4
22	Anu priya	28	47734	P	39	+	+	-	-	-	-	168/116	1+	SPIH	244	1.72	292	9.6	30.6
23	Sindhuja	28	48573	G2P1	39	-	-	-	-	-	-	110/76	-	NP	134	2.92	236	10.2	33.6
24	Aysha	29	6992	P	38	-	-	-	-	-	-	120/80	-	NP	188	1.64	352	10.4	30.8
25	Sanjana	23	8659	P	38	-	-	-	-	-	-	118/76	-	NP	132	2.12	468	11.2	35.8
26	Suba lakshmi	25	49655	P	37	-	-	-	-	-	-	122/78	-	NP	178	2.82	228	10.8	30.2
27	Banumathi	27	6876	G2P1	37	-	-	-	-	-	-	158/94	-	NSPIH	162	2.46	216	11.8	26.2
28	Sri devi	27	7385	P	37	-	-	-	-	-	-	118/70	-	NP	144	3.42	332	8.2	27.8
29	Kiruba	27	58765	P	38	-	-	-	-	-	-	120/80	-	NP	156	3.22	348	10.6	26.2
30	Lavanya	29	6749	P	38	+	+	-	-	-	-	170/110	Trace	SPIH	196	2.52	212	8.4	27.4
31	Subashini	25	8613	P	39	-	+	-	-	-	-	180/116	1+	SPIH	210	1.32	214	12.4	28.2

32	Vasuki	24	52314	G2P1	39	-	-	-	-	-	-	120/70	-	NP	154	3.38	398	10.4	24.6
33	Hari priya	23	55512	P	37	+	+	+	-	-	-	176/118	1+	SPIH	232	1.36	298	11.4	26.6
34	Preethi	25	42671	P	37	-	-	-	-	-	-	118/74	-	NP	168	2.96	344	10.2	26.8
35	Raja rajeshwari	24	76428	P	38	-	-	-	-	-	-	112/76	-	NP	148	3.84	386	13.4	27.2
36	Diana	25	56732	P	39	-	-	-	-	-	-	148/98	-	NSPIH	186	2.58	384	9.2	27.2
37	Abinaya	28	9543	G2P1	39	-	-	-	-	-	-	118/78	-	NP	170	3.12	342	11.4	27.8
38	Swathi priya	27	47614	G2P1	38	-	-	-	-	-	-	110/80	-	NP	132	3.26	392	11.4	27.4
39	Nandhini	25	32145	P	38	+	+	-	-	-	+	178/120	Trace	SPIH	238	1.24	218	10.4	29.2
40	Steffy	24	61634	G2P1	37	-	-	-	-	-	-	116/70	-	NP	148	2.46	354	11.2	26.6
41	Premalatha	23	34661	P	38	-	-	-	-	-	-	150/100	-	NSPIH	222	2.48	256	8.2	26.8
42	Kalaivani	28	43217	P	39	-	+	-	+	-	-	178/116	2+	SPIH	222	1.56	242	10.8	29.4
43	Viji	27	56903	P	39	-	-	-	-	-	-	112/70	-	NP	114	4.28	352	11.2	25.8
44	Priya	25	65934	P	39	+	+	-	-	-	+	168/120	1+	SPIH	256	0.92	256	11.6	39.4
45	Vadiukkarasi	24	87562	P	39	-	-	-	-	-	-	114/78	-	NP	164	2.8	462	11.4	30.2
46	Hemalatha	23	35791	G2P1	37	+	-	-	-	-	+	180/110	1+	SPIH	228	1.48	248	11.8	39.4
47	Varshini	23	4682	P	37	-	-	-	-	-	-	116/80	-	NP	210	2.84	312	13.2	25.6
48	Pravathi	23	60312	P	38	-	-	-	-	-	-	114/78	-	NP	134	1.82	356	10.2	29.2
49	Helan mary	27	8792	P	38	-	-	-	-	-	-	158/102	-	NSPIH	210	1.68	252	8.4	26.2
50	Jaya priyanka	25	37850	P	38	-	-	-	-	-	-	120/70	-	NP	174	3.42	356	12.2	24.2
51	Indhumathi	26	5129	P	39	-	-	-	-	-	-	148/100	-	NSPIH	172	1.72	254	8.6	29.2
52	Daisy	29	9296	G2P1	37	-	+	-	+	-	-	164/128	Trace	SPIH	242	0.88	244	12.8	38.4
53	Shasmitha	25	92778	P	37	-	-	-	-	-	-	110/80	-	NP	116	3.46	246	10.6	30.4
54	Aishwarya	24	7778	G2P1	39	-	+	-	-	+	+	170/118	Trace	SPIH	212	0.68	246	12.6	24.6
55	Naveena	22	7541	P	38	-	-	-	-	-	-	112/70	-	NP	188	0.64	378	12.6	30.6
56	Divya	23	36597	G2P1	37	-	-	-	-	-	-	156/100	-	NSPIH	178	1.58	256	8.2	29.6
57	Sowmiya	23	95855	P	39	-	-	-	-	-	-	110/80	-	NP	192	1.94	278	8.6	30.8
58	Deepa	24	8056	P	39	-	-	-	-	-	-	148/92	-	NSPIH	186	1.84	396	9.2	28.6
59	Latha	25	55441	P	39	-	-	-	-	-	-	112/70	-	NP	186	3.28	394	12.8	30.2
60	Suganya	25	9353	G2P1	38	+	+	-	-	-	-	170/110	3+	SPIH	240	0.78	256	13.6	25.6
61	Rekha	22	8453	P	38	-	+	-	-	-	+	172/128	4+	SPIH	252	2.58	252	13.8	27.2
62	Pradeepa	47	36751	P	37	-	-	-	-	-	-	120/80	-	NP	134	1.98	442	10.2	30.4
63	Manimegalai	25	37159	P	38	-	-	-	-	-	-	110/70	-	NP	182	4.18	298	12.6	29.6
64	Yasodha	24	42298	P	37	+	+	-	-	-	-	170/116	3+	SPIH	194	2.42	454	13.4	39.4
65	Sasi priya	23	38335	P	38	-	-	-	-	-	-	120/70	-	NP	172	1.68	238	12.8	29.8
66	Kavitha	22	6871	G2P1	37	+	+	-	-	-	-	174/112	4+	SPIH	198	1.48	296	13.2	27.6
67	Saranya	22	56654	G2P1	37	-	-	-	-	-	-	116/80	-	NP	128	3.52	298	10.8	35.6
68	Varsha	28	36521	P	37	-	+	-	-	-	+	180/120	3+	SPIH	258	2.36	258	13.8	22.2
69	Praveena	27	70803	P	37	-	-	-	-	-	-	148/96	-	NSPIH	202	2.56	344	9.8	30.6
70	Narmadha	22	46132	P	39	-	+	-	-	+	-	170/128	3+	SPIH	234	2.22	292	13.6	23.2
71	Niraja	25	31875	P	38	-	-	-	-	-	-	120/80	-	NP	122	2.12	292	11.8	31.2
72	Nishanthini	24	31487	P	37	-	-	-	-	-	-	110/80	-	NP	158	3.82	372	11.2	31.4
73	Shanthi	24	58125	P	39	+	+	-	-	-	+	178/116	-	SPIH	226	2.34	248	13.2	39.4
74	Savitha	24	9512	P	38	-	+	-	-	+	-	180/110	4+	SPIH	200	1.92	278	12.6	39.2
75	Revathi	22	51295	P	38	+	+	-	-	-	-	190/120	3+	SPIH	248	0.86	276	12.8	39.6

76	Viveena	26	38870	P	38	-	-	-	-	-	-	120/80	-	NP	160	4.26	272	13.8	34.6
77	Nivetha	24	8592	G2P1	38	-	-	-	-	-	-	148/94	-	NSPIH	182	3.24	356	9.2	30.2
78	Sindhu	26	5668	P	39	-	-	-	-	-	-	110/70	-	NP	124	1.62	268	13.2	33.6
79	Brindha	27	6573	P	37	-	-	-	-	-	-	150/100	-	NSPIH	200	2.48	358	10.4	30.4
80	Boomika	25	51185	G2P1	37	-	-	-	-	-	-	110/80	-	NP	158	1.82	262	13.6	32.6
81	Sowmiya	23	51092	G2P1	38	-	-	-	-	-	-	146/100	-	NSPIH	174	2.3	258	10.2	30.2
82	Ramya	24	52993	P	39	-	-	-	-	-	-	150/92	-	NSPIH	148	2.82	312	10.6	29.2
83	Vaishnavi	24	8197	G2P1	39	-	-	-	-	-	-	116/74	-	NP	136	1.74	246	13.8	33.6
84	Dharshana	22	42893	P	39	+	+	-	-	-	-	162/116	2+	SPIH	206	0.98	288	12.6	34.8
85	Divya dharshini	22	51296	P	38	-	-	-	-	-	-	110/70	-	NP	134	3.72	232	12.4	34.6
86	Pavithra	22	45678	P	37	+	+	-	-	-	+	176/112	2+	SPIH	212	1.84	282	12.2	35.2
87	Mala	22	7843	G2P1	37	-	-	-	-	-	-	156/98	-	NSPIH	158	2.22	388	11.2	31.2
88	Vikashini	23	32689	P	37	-	-	-	-	-	-	150/100	-	NSPIH	156	1.78	248	11.4	31.4
89	Subu lakshmi	24	33109	P	38	-	-	-	-	-	-	110/70	-	NP	130	2.62	252	9.2	35.6
90	Sathya	25	32194	G2P1	37	-	-	-	-	-	-	152/98	Trace	NSPIH	176	1.8	294	9.6	31.6
91	Saroja	28	6779	G2P1	37	-	-	-	-	-	-	120/74	-	NP	134	3.32	236	11.8	35.4
92	Sangeetha	26	9666	P	37	+	+	-	-	-	+	170/116	2+	SPIH	192	1.52	312	11.4	37.4
93	Priya dharshini	23	8437	G2P1	37	-	-	-	-	-	-	116/78	-	NP	172	3.28	254	9.6	35.8
94	Shruthi	25	9487	P	39	-	-	-	-	-	-	150/108	Trace	NSPIH	158	1.92	314	11.8	31.8
95	Mallika	27	7895	P	38	-	-	-	-	-	-	112/76	-	NP	140	2.22	242	11.2	32.6
96	Kalai selvi	26	6554	P	39	-	-	-	-	-	-	146/106	-	NSPIH	206	1.96	268	11.2	32.2
97	Chitra devi	23	35552	P	38	-	-	-	-	-	-	114/80	-	NP	130	2.86	238	10.6	32.2
98	Seetha	25	9047	P	38	-	-	-	-	-	-	148/104	Trace	NSPIH	184	2.42	294	11.8	33.2
99	Maha lakshmi	22	8554	P	38	-	-	-	-	-	-	120/76	-	NP	158	2.72	244	10.4	34.2
100	Indhra	25	9566	G2P1	38	-	-	-	-	-	-	140/100	1+	NSPIH	182	2.52	298	10.8	33.4
101	Janani	23	6935	P	37	-	-	-	-	-	-	118/74	-	NP	140	3.24	288	10.2	32.8
102	Suba	23	39412	P	38	+	+	-	-	-	+	174/120	2+	SPIH	252	1.22	354	14.8	35.2
103	Raja kumari	23	8015	P	39	-	-	-	-	-	-	144/102	-	NSPIH	170	2.56	272	10.2	34.2
104	Selvi	28	6485	P	38	-	-	-	-	-	-	146/100	-	NSPIH	160	1.96	298	11.2	34.2
105	Sujitha	24	9894	P	38	-	-	-	-	-	-	120/80	-	NP	164	2.82	296	11.8	31.2
106	Priya	25	6684	P	38	+	+	-	-	-	-	176/110	2+	SPIH	216	2.48	348	14.8	37.2
107	varshini	25	5601	P	37	-	-	-	-	-	-	116/80	-	NP	116	3.36	456	9.4	25.8
108	Subraja	24	9585	G2P1	37	-	-	-	-	-	-	150/96	Trace	NSPIH	156	2.64	292	13.8	33.6
109	Narmadha	23	50083	G2P1	37	-	-	-	-	-	-	120/70	Trace	NP	178	3.4	254	11.2	24.6
110	Aysha rifana	23	8098	G2P1	38	+	+	-	-	+	-	180/120	2+	SPIH	232	1.58	368	18.2	34.8
111	Sujatha	23	11557	P	38	-	-	-	-	-	-	110/80	-	NP	182	3.46	224	11.4	24.8
112	Sathya	24	8870	P	38	+	+	-	+	-	-	170/110	1+	SPIH	252	1.86	398	18.4	33.4
113	Gayathri	25	8708	P	39	-	-	-	-	-	-	118/70	-	NP	156	3.28	272	10.8	24.2
114	Anisha	25	7987	P	39	+	+	-	-	-	-	176/112	1+	SPIH	204	1.78	424	18.6	32.2
115	Kowsalya	25	9565	P	38	-	-	-	-	-	-	116/74	-	NP	152	2.66	252	10.4	22.2
116	Pavithra	22	50708	P	38	-	-	-	-	-	-	148/96	-	NSPIH	182	2.12	278	13.2	34.6
117	Priyanka	23	36640	G2P1	37	-	-	-	-	-	-	118/72	-	NP	174	2.72	288	11.2	23.2
118	Kalyani	27	34723	G2P1	38	-	-	-	-	-	-	144/92	-	NSPIH	228	3.48	292	12.4	35.6
119	Rohini	26	5486	P	38	-	-	-	-	-	-	110/72	-	NP	112	2.68	424	8.4	24.8

120	Seema	23	9726	P	37	+	+	-	+	-	-	184/114	1+	SPIH	224	0.76	378	19.8	31.2